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| (21) International Application Number: PCT/US99/15710 (22) International Filing Date: 12 July 1999 (12.07.99) (30) Priority Data: 09/123,168 27 July 1998 (27.07.98) US (71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US). (72) Inventors: SHUTTER, John, R.; 13175 Silver Creek Street, Moorpark, CA 93021 (US). STARK, Kevin, L.; 777 Emerson Street, Thousand Oaks, CA 91362 (US). (74) Agents: ODRE, Steven, M. et al.; Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US). | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i> | |
| (54) Title: DELTA-RELATED POLYPEPTIDES <p style="text-align: center;"> MAAASRSASG WALLLLVALW QQRAAGSGVF QLQLQEFINE RGVLASGRPC EPGCRTFFRV CLKHFQAVVS PGPCTFGTVS TPLVLTNSFA VRDDSSGGGR NPLQLPFNFT WPGTFSLIE AWHAPGDDL R PEALPPDALI SKIAIQGSLA VGQNWLLDEQ TSTLTRLYS YRVICSDNY GDNCSRLCKK RNDHFGHYVC QPDGNSCLP GWTGEYCQP ICLSGCHEQN GYCSKPAECL CRPGWQGRLC NECIPHNGCR HGTCSTPWQC TCDEGWGGLF CDQDLNYCTH HSPCKNGATC SNSGQRSYTC TCRPGYTGVD CELELSECD NPCRNGGSCK DQEDGYHCLC PPGYYGLHCE HSTLSCADSP CFNGGSCRER NQGANYACEC PPNFTGSNCE KKVDRCTSNP CANGGQCLNR GPSRMCRCRP GFTGTYCELH VSDCARNPCA HGGTCHDLEN GLMCTCPAGF SGRRCEVRTS IDACASSPCF NRATCYTDLS TDTFVCNCPY GFVGSRCFPP VGLPPSPFWV <u>AVSLGVQLAV</u> <u>LLVLLGVAV</u> <u>AVRQLRLRRP</u> DDGSREAMNN LSDFQKDNLI PAAQLKNTNQ KKELEVDCGL DKSNCGKQON HTLDYNLAPG PLGRGTMPGK FPHSDKSLGE KAPLRLHSEK PECRISAICS PRDSMYQSV LISEERNECV IATEV </p> | | |
| (57) Abstract Nucleic acid sequences are disclosed which encode polypeptide members of the Delta family of mammalian membrane surface-bound ligands; such sequences can be used, among other things, for chromosome mapping and analysis and to produce the polypeptides in abundance by recombinant expression of the corresponding DNA molecules. | | |

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DELTA-RELATED POLYPEPTIDESFIELD OF THE INVENTION

5 This invention relates to novel mammalian polypeptide members of the cell development cycle protein family known as "Delta", to the corresponding nucleic acids, and to methods of making and using the nucleic acid molecules and polypeptides.

10

BACKGROUND OF THE INVENTION

 The Notch gene family encodes transmembrane receptors that control cell fate decisions; see review
15 in Fleming et al., Trends in Cell Biology, Volume 7, pages 437-441 (1997). Currently, there are at least four known members of this family in the human, which are designated as Notch1, Notch2, Notch3 and Notch4; for reference, see Ellisen et al., Cell, Volume 66,
20 pages 649-661 (1991); Katsanis et al., Genomics, Volume 35, pages 101-108 (1996); Joutel et al., The Lancet, Volume 350, pages 1511-1515 (1997); and Uyttendaele et al., Development, Volume 122, pages 2251-2259 (1996), respectively. Many of the known actions of Notch
25 signaling have been documented during the development of lower organisms, such as worms and flies, but increasing attention is now being devoted to the role that these receptors may play during mammalian embryogenesis; Lewis, Current Opinion in Neurobiology,
30 Volume 6, pages 3-10 (1996). However, relatively little is known about the function of these receptors in the biology of the adult mammal at present.

The activation of the Notch receptors can be accomplished by ligands belonging to the Delta and Jagged gene families. These gene products also contain transmembrane domains, and the interaction of the
5 ligand with the receptor most likely occurs via cell to cell contact. Perhaps the most well-documented case of Delta-Notch signaling occurs in the production of neural precursor cells in *Drosophila*. Since the absence of Delta-Notch signaling results in an
10 excessive production of neuronal cells, this signaling pathway is thought to inhibit the differentiation of precursors in a process known as lateral specification; see Lewis, above. This process allows a defined population of cells to adopt one particular cell fate,
15 while allowing adjacent cells to avoid that commitment.

There have been two Delta ligands reported for the mouse, namely, Delta-like 1 (also referred to as "Dll1") and Delta-like 3 (also referred to as "Dll3").
20 These genes are primarily expressed in the neuroectoderm and the presomitic mesoderm, and are thought to function in the formation of the nervous and musculoskeletal systems; see Dunwoodie et al., Development, Volume 124, pages 3065-3076 (1997).

25

SUMMARY OF THE INVENTION

This invention is based on the discovery and isolation of novel nucleic acids encoding polypeptides
30 from mouse and human species which can be considered members of the Delta family of ligands.

Previously, vertebrate Notch ligands have been divided into two classes: Delta and Serrate; see Nye
35 and Kopan, Current Biology, Volume 5, Number 9, pages 966-969 (1995). The polypeptide members of both

families contain a signal sequence, an amino-terminal Delta-Serrate-Lag (DSL) domain, a series of EGF-like repeats, and a single transmembrane (hydrophobic) domain. The Serrate family members also contain a
5 cysteine-rich region in the extracellular portion and inserts that interrupt some of the EGF-like repeats. Characteristic of the Delta class, full length polypeptides in accordance with the present invention contain a signal sequence, a DSL domain, EGF-like
10 repeats, and a transmembrane domain, but do not contain inserts that interrupt some of the EGF-like repeats or an extracellular cysteine-rich region. Moreover, the amino acid sequence of the present murine polypeptide is approximately fifty percent identical to that of
15 murine Dll1 and, like Dll1, contains eight EGF-like repeats. Consequently, the polypeptides of this invention can be considered members of the Delta family.

20 The highly specific expression pattern of the newly discovered murine gene within vascular endothelium, coupled with the known actions of other members of the Delta family, indicate a role for the present polypeptides in the control of endothelial cell
25 biology.

Studies relating to Notch-Delta signaling in non-human species indicate that such receptor-ligand interactions are central to vertebrate neurogenesis and
30 influence the development of precursor cells for the retina and central nervous system; Nye et al., Current Biology, and Lewis, Current Opinion in Neurobiology, above. Other studies suggest that Notch signaling is also involved in the regulation of fibroblast growth
35 factor-induced angiogenesis; Zimrin et al., Journal of Biological Chemistry, Volume 271, Number 51, pages

32499-32502 (1996). Moreover, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), an autosomal dominant disorder that causes ischaemic strokes in adults, has recently been traced to a mutational defect in the Notch3 gene. Joutel et al., Lancet, above.

Based on such information, the current understanding of Notch behavior has lead to the belief that Notch controls the ability of precursor cells to progress to the next differentiated state, most likely through interaction with ligands such as Delta, among others. Thus, Delta polypeptides are thought to play a key role in cell development. Moreover, the possibility that malfunctions in Notch-Delta signaling and the Delta genes may result in one or more diseases or disorders suggests fertile ground for further research and study.

In view of the foregoing, the full length DNA sequences given herein, or subsequences thereof, may be used for chromosome identification and gene mapping (not unlike an EST), which is a utility of the present invention. In such applications, a key objective would be to determine whether the gene falls within a known area of a chromosome linked to a genetic disease or disorder, and whether the gene itself is responsible for the abnormality. Such studies can be carried out with the murine as well as human sequences. For instance, information regarding the murine gene and its biology may be useful for understanding the human gene if abnormalities associated with the gene in mice have counterparts in humans.

Other potential uses for the molecules of this invention are delineated further below, including use

of the polypeptides to identify a corresponding receptor or receptors (possibly in the Notch family). Still other uses of the nucleic acid and polypeptide molecules of this invention will become clearer over
5 time, based on further elucidation of the biological activity of the polypeptides of this invention, particularly in light of the present description.

This invention also includes biologically active
10 fragments and analogs of the aforementioned polypeptides, DNA molecules encoding such fragments and analogs, as well as derivatives of such polypeptides as further described below.

15 Additionally, this invention includes vectors for the recombinant expression of the above mentioned nucleic acid molecules in heterologous host cells, as well as host cells which have been modified (e.g., by transfection or transformation) to contain such
20 expression vectors.

In addition, this invention comprises methods for the recombinant production of the polypeptides, fragments and analogs mentioned above, including the
25 steps of expressing the polypeptide, fragment or analog encoded by a DNA molecule in a host cell and collecting the resulting expression product.

As a still further aspect of the invention, the
30 present polypeptides can be used in methods and systems for the identification of receptors which bind to and/or are activated by the polypeptides. Such receptors may be found, for instance, on the surface of adjacent cells that come into contact or proximity with
35 the present polypeptides, which are membrane bound in their naturally occurring state.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 (A-B). This figure depicts the DNA sequence encoding a murine polypeptide of this invention. The portion encoding the transmembrane region of the murine polypeptide is underlined.

FIGURE 2. This figure depicts the amino acid sequence for the murine polypeptide encoded by the DNA molecule of Figure 1A-1B, including a putative signal peptide region (amino acids 1-22, 1-23, 1-24, 1-25, 1-26, or 1-27), a putative extracellular domain (amino acids 23-532, 24-532, 25-532, 26-532, 27-532, or 28-532), a transmembrane region (amino acids 533-553), and an intracellular/cytoplasmic portion (amino acids 554-686). The transmembrane region is underlined.

FIGURE 3 (A-B). This figure depicts the DNA sequence encoding a human polypeptide of this invention. The portion encoding the transmembrane region of the polypeptide is underlined.

FIGURE 4. This figure depicts the amino acid sequence for the human polypeptide encoded by the DNA molecule of Figure 3A-3B, including a putative signal peptide region (amino acids 1-23, 1-24, 1-25, or 1-26, 1-27, or 1-28), a putative extracellular domain (amino acids 24-531, 25-531, 26-531, 27-531, 28-531, or 29-531), a transmembrane region (amino acids 532-552), and an intracellular/cytoplasmic portion (amino acids 553-685). The transmembrane region is underlined.

FIGURE 5 (A-P). This figure depicts the expression pattern of messenger RNA (mRNA) for the murine polypeptide in various adult mouse tissues, as

analyzed by *in situ* hybridization using a ^{33}P -labeled riboprobe.

FIGURE 6 (A-P). This figure depicts the
5 expression pattern of mRNA for the murine polypeptide
in various adult mouse tissues, as analyzed by *in situ*
hybridization using a ^{33}P -labeled riboprobe.

FIGURE 7 (A-D). This figure depicts the
10 expression pattern of mRNA for the murine polypeptide
in mouse embryos at ten and one-half days (Figs. A and
B) and eleven and one-half days (Figs. C and D) after
fertilization, as analyzed by *in situ* hybridization
using a ^{33}P -labeled riboprobe.

15

DETAILED DESCRIPTION OF THE INVENTION

As indicated, a novel member of the human Delta
20 family, and its murine counterpart, are provided by
this invention. This discovery resulted from the
identification of polymerase chain reaction (PCR)
fragments isolated from a murine white adipose tissue
cDNA library. As illustrated by the working examples
25 given further below, the PCR fragments enabled the
identification of the full length nucleic acid sequence
encoding the murine polypeptide of this invention (SEQ
ID NO: 1) and its predicted amino acid sequence (SEQ ID
NO: 2). Probes prepared from the murine sequence were
30 then used to screen a human brain cDNA library, leading
to the isolation and identification of a full length
nucleic acid sequence (SEQ ID NO: 3) encoding a
counterpart human polypeptide (SEQ ID NO: 4).

35 Using hydrophobicity analysis, the leader
("signal") sequence for the murine polypeptide is

likely to comprise amino acids 1-22, 1-23, 1-24, 1-25, 1-26, 1-27, or 1-27. The first amino acid of the "mature" polypeptide is likely to be 23 (Q), 24 (R), 25 (A), 26 (A), 27 (G), or 28 (S). The beginning of the transmembrane domain appears to be located at position 533 (V). The end of the transmembrane domain appears to be located at position 553 (V). At a minimum, what is needed for biological activity is the extracellular domain of the mature polypeptide, specifically, amino acids 23 (Q), 24 (R), 25 (A), 26 (A), 27 (G), or 28 (S) through amino acid 532 (A). Thus, murine polypeptides in accordance with this invention will include any of those having the following amino acids:

- | | | | |
|----|-----|--------|----------------------|
| 15 | (a) | 1-686 | (SEQ ID NO: 2), |
| | (b) | 23-532 | (SEQ ID NO: 5), |
| | (c) | 24-532 | (SEQ ID NO: 6), |
| | (d) | 25-532 | (SEQ ID NO: 7), |
| | (e) | 26-532 | (SEQ ID NO: 8), |
| 20 | (f) | 27-532 | (SEQ ID NO: 9), |
| | (g) | 28-532 | (SEQ ID NO: 10) |
| | (h) | 23-553 | (SEQ ID NO: 11), |
| | (i) | 24-553 | (SEQ ID NO: 12), |
| | (j) | 25-553 | (SEQ ID NO: 13), |
| 25 | (k) | 26-553 | (SEQ ID NO: 14), |
| | (l) | 27-553 | (SEQ ID NO: 15), |
| | (m) | 28-553 | (SEQ ID NO: 16), |
| | (n) | 23-686 | (SEQ ID NO: 17), |
| | (o) | 24-686 | (SEQ ID NO: 18), |
| 30 | (p) | 25-686 | (SEQ ID NO: 19), |
| | (q) | 26-686 | (SEQ ID NO: 20), |
| | (r) | 27-686 | (SEQ ID NO: 21), and |
| | (s) | 28-686 | (SEQ ID NO: 22) |

35 with or without an amino(N)-terminal methionyl residue (-1).

The leader ("signal") sequence for the human polypeptide is likely to comprise amino acids 1-23, 1-24, 1-25, 1-26, 1-27 or 1-28. The first amino acid of the "mature" polypeptide is likely to be 24 (A), 25 (A), 26 (G), 27 (S), or 28 (G), or 29 (V). The beginning of the transmembrane domain appears to be located at position 532 (V). The end of the transmembrane domain appears to be located at position 552 (V). At a minimum, what is needed is the extra-cellular domain of the "mature" polypeptide, specifically, amino acids 24 (A), 25 (A), 26 (G), 27 (S), or 28 (G), or 29 (V) through amino acid 531 (A). Therefore, the human polypeptides of this invention include those having the following amino acids:

- | | | | |
|----|-----|--------|----------------------|
| | (a) | 1-685 | (SEQ ID NO: 4), |
| | (b) | 24-531 | (SEQ ID NO: 23), |
| | (c) | 25-531 | (SEQ ID NO: 24), |
| 20 | (d) | 26-531 | (SEQ ID NO: 25), |
| | (e) | 27-531 | (SEQ ID NO: 26), |
| | (f) | 28-531 | (SEQ ID NO: 27), |
| | (g) | 29-531 | (SEQ ID NO: 28), |
| | (h) | 24-552 | (SEQ ID NO: 29), |
| 25 | (i) | 25-552 | (SEQ ID NO: 30), |
| | (j) | 26-552 | (SEQ ID NO: 31), |
| | (k) | 27-552 | (SEQ ID NO: 32), |
| | (l) | 28-552 | (SEQ ID NO: 33), |
| | (m) | 29-552 | (SEQ ID NO: 34), |
| 30 | (n) | 24-685 | (SEQ ID NO: 35), |
| | (o) | 25-685 | (SEQ ID NO: 36), |
| | (p) | 26-685 | (SEQ ID NO: 37), |
| | (q) | 27-685 | (SEQ ID NO: 38), |
| | (r) | 28-685 | (SEQ ID NO: 39), and |
| 35 | (s) | 29-685 | (SEQ ID NO: 40) |

with or without an N-terminal methionyl residue (-1).

Tissue distribution analysis in mice (Example 5, below) demonstrates that the presence of nucleic acids encoding the polypeptide is fairly ubiquitous, with gene expression being highest in the lung, followed by heart, kidney, skeletal muscle and brain, and to a lesser extent, the spleen and testis.

10 The present invention provides purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and biological activity) and physical properties (e.g., molecular weight) of the naturally-occurring (human and murine) polypeptides of this invention, including allelic variants thereof. The term "purified and isolated" herein means substantially free of unwanted substances so that the present polypeptides are useful for an intended purpose. For example, one may have a recombinant polypeptide substantially free of other human (or murine) proteins or pathological agents. These polypeptides are also characterized by being a product of mammalian cells, or the product of chemical synthetic procedures or of prokaryotic or eukaryotic host expression (e.g., by bacterial, yeast, higher plant, insect and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis. The products of expression in typical yeast (e.g., *Saccharomyces cerevisiae*), insect, or prokaryote (e.g., *E. coli*) host cells are free of association with any mammalian proteins. The products of expression in vertebrate (e.g., non-human mammalian such as COS or CHO, and avian) cells are free of association with any human (or

murine) proteins. Depending upon the host employed, and other factors, polypeptides in accordance with this invention may be glycosylated with mammalian or other eukaryotic carbohydrates or may be non-glycosylated.

5 One may modify the nucleic acid so that glycosylation sites are included in the resultant polypeptide. One may choose to partially or fully deglycosylate a glycosylated polypeptide. The polypeptides may also include an initial methionine amino acid residue (at

10 position -1 with respect to the first amino acid residue of the mature polypeptide).

In addition to naturally-occurring allelic forms of the polypeptide, the present invention also embraces

15 other products such as polypeptide analogs. For instance, modifications of cDNA and genomic genes may be readily accomplished by well-known site-directed mutagenesis techniques and employed to generate analogs which differ in the primary conformations herein

20 specified in terms of the identity or location of one or more residues (e.g., substitutions; terminal and intermediate additions and deletions). Such products would share at least one of the biological properties of the naturally occurring polypeptide but may differ

25 in others. As examples, projected products of the invention include those which are foreshortened by e.g., deletions (i.e., fragments or subsequences); or those which are more stable to hydrolysis (and, therefore, may have more pronounced or longer lasting

30 effects than naturally-occurring); or which have been altered to delete one or more potential sites for glycosylation (which may result in higher activities for yeast-produced products); or which have one or more cysteine residues deleted or replaced by, e.g., alanine

35 or serine residues and are potentially more easily isolated in active form from microbial systems; or

which have one or more tyrosine residues replaced by phenylalanine; or have an altered lysine composition (such as those prepared for purposes of derivatization). Included are those polypeptides with amino acid substitutions which are conservative according to acidity, charge, hydrophobicity, polarity, size, or any other characteristic known to those skilled in the art. One may make changes in selected amino acids so long as such changes preserve the overall folding or activity of the protein, as discussed in greater detail further below. Small amino terminal extensions, such as an amino-terminal methionine residue, a small linker peptide of up to about 20-25 residues, or a small extension that facilitates purification, such as a poly-histidine tract, an antigenic epitope or a binding domain, may also be present. See, in general, Ford et al., Protein Expression and Purification Volume 2, pages 95-107 (1991).

20

One may also prepare soluble forms of the polypeptides of (a) above, human or murine, by elimination of the transmembrane and intracellular regions; see (b), above, in this regard.

25

Of particular interest herein is the human polypeptide (SEQ ID NO: 4) and its fragments, analogs and derivatives, as well as DNA molecules encoding such polypeptides. However, as will be seen, the murine counterpart (SEQ ID NO: 2) may also be useful for the same or similar purposes.

30

Polypeptide Analogs

35

In addition to the polypeptides of the particular sequences delineated above, and fragments thereof, also

intended as part of this invention are analogs of such polypeptides which are biologically equivalent or share one or more biological properties. By "biologically equivalent" is meant having the same properties of the polypeptides described herein. Preferably, such analogs will cross-react with antibodies raised against the polypeptide of SEQ ID NO: 4 (or of SEQ ID NO: 2).

The term "analog" as applied to the polypeptides of this invention is specifically intended to mean molecules representing one or more amino acid substitutions, deletions and/or additions derived from the linear array of amino acids of the full length polypeptide SEQ ID NO: 4 (or of SEQ ID NO: 2), and which are also substantially biologically equivalent or share one or more biological properties.

Especially preferred polypeptide analogs in accordance with this invention are those which possess a degree of homology (i.e., identity of amino acid residues) with the polypeptide of SEQ ID NO: 4 (or of SEQ ID NO: 2) or in excess of eighty percent (80%), and most preferably, in excess of ninety percent (90%) or ninety-five (95%).

25

Percent sequence identity can be determined by standard methods that are commonly used to compare the similarity the amino acids of two polypeptides in order to generate an optimal alignment of two respective sequences. By way of illustration, using a computer algorithm such as BLAST, BLAST2, or FASTA, the two polypeptides for which the percent identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span", which can include the full length of one or both sequences, or along a pre-determined portion of one or both

sequences). Each computer algorithm provides a "default" opening penalty and a "default" gap penalty, and a scoring matrix such as PAM 250 (for FASTA) or BLSUM 62 (for BLAST algorithms). A preferred algorithm
5 for the purposes of this invention is BLAST2.

A standard scoring matrix can be used in conjunction with the computer algorithm; see Dayhoff et al. in Atlas of Protein Sequence and Structure, Volume
10 5, Supplement 3 (1978). The percent identity can then be determined using an algorithm such as contained in FASTA, as follows:

$$\frac{\text{Total number of identical matches}}{[\text{Length of the longer sequence within the matched span}] + [\text{Number of gaps introduced into the longer sequence in order to align the two sequences}]} \times 100$$

15

Analog polypeptides in accordance with this invention that are at least eighty percent identical to "wild type" sequence of Figure 4 (or of Figure 2) will typically have one or more amino acid substitutions, deletions and/or insertions, compared with the wild
20 type. Usually, the substitutions will be conservative so as to have little or no effect on the overall net charge, polarity or hydrophobicity of the polypeptide. Examples of conservative substitutions are set forth
25 below.

Table 1Conservative Amino Acid Substitutions

| | |
|--------------|---------------|
| Basic: | arginine |
| | lysine |
| | histidine |
| Acidic: | glutamic acid |
| | aspartic acid |
| Polar: | glutamine |
| | asparagine |
| Hydrophobic: | leucine |
| | isoleucine |
| | valine |
| Aromatic: | phenylalanine |
| | tryptophan |
| | tyrosine |
| Small: | glycine |
| | alanine |
| | serine |
| | threonine |
| | methionine |

5

When making substitutions (or omissions) of particular amino acid residues within the naturally occurring (i.e., "native") amino acid sequence of the wild type, relatively conservative substitutions are preferred so as not to adversely affect desired biological properties to any substantial degree. Thus, for example, residues or regions which are known or suspected to be involved in receptor specificity or heparin binding should generally be avoided if alterations in these sites will detract from these properties.

10

15

In general, polypeptide fragments and analogs in accordance with this invention will be useful for the same purposes for which the polypeptide of SEQ ID NO: 4 (or SEQ ID NO: 2) is useful.

5

Nucleic Acids

According to another aspect of the present invention, the DNA sequences described herein which encode the polypeptides are useful in generating new and useful DNA vectors, transformed and transfected prokaryotic and eukaryotic host cells (including bacterial cells, yeast cells, insect cells, and mammalian cells grown in culture), and methods for cultured growth of such host cells capable of expression of the polypeptides and related products.

In addition to (a) the DNA molecules of Figure 1A-1B (SEQ ID NO: 1) and Figure 3A-3B (SEQ ID NO: 3), also intended as part of this invention are (b) naturally occurring allelic variants thereof which encode the same polypeptides, (c) DNA molecules which selectively hybridize to any such DNA sequences, and (d) DNA molecules which, but for the degeneracy of the genetic code, would hybridize to any DNA of (a), (b) and (c).

Complementary sequences of the foregoing DNA molecules, or subsequences thereof, may be used to screen cDNA or genomic libraries to isolate the nucleic acid molecules of SEQ ID NO: 1 and SEQ ID NO: 3 and naturally occurring allelic variants thereof for use in recombinant expression (or for modification as described below). Alternatively, nucleic acid molecules encoding the same polypeptides can be made prepared by chemical synthesis using methods well known

to the skilled artisan, such as those described by Engels et al. in Angew. Chem. Intl. Ed., Volume 28, pages 716-734 (1989). Such methods include, inter alia, the phosphotriester, phosphoramidite and H-phosphonate methods for nucleic acid synthesis. A preferred method involves polymer supported synthesis using standard phosphoramidite chemistry. Usually, DNA molecules encoding the polypeptides of this invention will be several hundred nucleotides in length. Nucleic acid molecules larger than about one hundred nucleotides can be synthesized as several fragments in accordance with these methods, and the fragments can then be ligated together to form a full-length molecule encoding the entire polypeptide.

15

Optionally, the portion of DNA encoding the amino (N) terminus of the polypeptide will contain an "ATG" codon, which encodes a methionine residue.

20

Variant nucleic acid molecules having sequences which differ from the naturally occurring ones and encode polypeptide analogs in accordance with this invention may be produced using site specific mutagenesis, PCR amplification, or other appropriate methods known to those skilled in the art; see, for instance, Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1989). Such variants would also include those containing nucleotide substitutions accounting for codon preference in the host cell being employed for expression.

25
30

The present invention also embraces nucleic acid molecules that may encode additional amino acid residues flanking the 5' or 3' portions of the region encoding the "mature" polypeptide (that is, the

35

processed expression product harvested from the host),
such as sequences encoding alternative pre/pro regions
(that is, sequences responsible for secretion of the
polypeptide through cell membranes) in place of the
5 "native" pre/pro regions. The additional sequences may
also constitute noncoding sequences, including
regulatory sequences such as promoters of transcription
or translation, depending on the host cell. The
nucleic acid molecules may even include various
10 internal non-coding sequences (introns) known to occur
within genes.

The nucleic acid molecules of this invention
(whether genes or cDNAs) can be inserted into a
15 suitable expression or amplification vector using
standard ligation techniques. The vector is selected
to be functional in the particular host employed (i.e.,
the vector is compatible with the host cell machinery,
such that amplification and/or expression of the
20 nucleic acid encoding the polypeptide can occur). The
polypeptide, fragment or analog may be amplified or
expressed in prokaryotic, yeast, insect (baculovirus
systems) and/or eukaryotic host cells, or in transgenic
non-human animal species as the host. Selection of the
25 host cell will depend at least in part on whether the
polypeptide expression product is to be glycosylated
and/or phosphorylated. If glycosylation and/or
phosphorylation is desired, then yeast, insect or
mammalian host cells are preferred for use, in that
30 yeast cells will glycosylate the polypeptide, and
insect and mammalian cells can glycosylate and/or
phosphorylate the polypeptide in a manner similar to
"native" glycosylation and/or phosphorylation.

35 The vectors used in any of the host cells to
express the polypeptide may also contain a 5' flanking

sequence (also referred to as a "promoter") and other expression regulatory elements operatively linked to the nucleic acid molecule (DNA) to be expressed, as well as enhancer(s), an origin of replication element, a transcriptional termination element, a complete intron sequence containing a donor and acceptor splice site, a signal peptide sequence, a ribosome binding site element, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element, as discussed in greater detail further below.

5' Flanking Sequence

The 5' flanking sequence may be the native 5' flanking sequence, or it may be homologous (i.e., from the same species and/or strain as the host), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of 5' flanking sequences from more than one source), or synthetic. The source of the 5' flanking sequence may be any unicellular prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the 5' flanking sequence is functional in, and can be activated by, the host cell machinery.

The 5' flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, 5' flanking sequences useful herein other than the flanking sequence will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of the 5'

flanking sequence may be known. In such a case, the 5' flanking sequence may be synthesized using the methods described above.

5 Where all or only a portion of the 5' flanking sequence is known, it may be obtained using PCR and/or by screening a genomic library with suitable oligonucleotide and/or 5' flanking sequence fragments from the same or another species. Where the 5'
10 flanking sequence is not known, a fragment of DNA containing a 5' flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction
15 endonuclease digestion using one or more carefully selected enzymes to isolate the proper DNA fragment. After digestion, the desired fragment may be isolated by agarose gel purification, or by other methods known to the skilled artisan. Selection of suitable enzymes
20 to accomplish this purpose will be readily apparent to one skilled in the art.

Origin of Replication Element

25 The origin of replication element is typically a part of prokaryotic expression vectors purchased commercially, and aids in the amplification of the vector in a host cell. Amplification of the vector to a certain copy number can, in some cases, be important
30 for optimal expression of the polypeptide. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence and then ligated into the vector.

Transcription Termination Element

The transcription termination element is typically located 3' to the end of the polypeptide coding sequence and serves to terminate transcription of the polypeptide. Usually, the transcription termination element in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the element is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those referred to above.

Selectable Marker Element

A selectable marker gene element encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, for example, ampicillin, tetracycline or kanamycin for prokaryotic host cells, (b) complement auxotrophic deficiencies of the cell, or (c) supply critical nutrients not available from complex media. Preferred selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene.

Ribosome Binding Element

The ribosome binding element, commonly called the Shine-Dalgarno sequence (for prokaryotes) or the Kozak sequence (for eukaryotes), is necessary for the initiation of translation for mRNA. The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be synthesized.

The Shine-Dalgarno sequence is varied but is typically a polypurine (i.e., having a high A-G content). Many Shine-Dalgarno sequences have been identified, each of which can be readily synthesized using methods referred to above and used in a prokaryotic vector.

Signal Peptide Sequence

In those cases where it is desirable for the polypeptide to be secreted from the host cell, a signal sequence may be used to direct the polypeptide out of the host cell, and the carboxy(C)-terminal part of the polypeptide may be deleted in order to prevent membrane anchoring. Typically, the signal sequence is positioned in the coding region of the nucleic acid sequence, or directly at the 5' end of the coding region. Many signal sequences have been identified, and any that are functional in the selected host cell may be used.

Transcription Promoter

Transcription of the gene may be enhanced by the presence of one or more introns in the vector. This is particularly true where the polypeptide is produced in eukaryotic host cells, especially mammalian host cells. The introns used may be naturally occurring within the gene, especially where the gene used is a full length genomic sequence or a fragment thereof. Where the intron is not naturally occurring within the gene (as is the case for most cDNAs), the intron(s) may be obtained from another source. The position of the intron with respect to the 5' flanking sequence and the encoding nucleic acid sequence is generally important, as the intron must be transcribed to be effective. As

such, where the nucleic acid is a cDNA molecule, the preferred position for the intron is 3' to the transcription start site, and 5' to the polyA transcription termination sequence. Preferably, the intron will be located on one side or the other (i.e., 5' or 3') of the cDNA such that it does not interrupt this coding sequence. Any intron from any source, including any viral, prokaryotic and eukaryotic (plant or animal) organisms, may be used, provided that it is compatible with the host cell into which it is inserted.

Where one or more of the elements set forth above are not already present in the vector to be used, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the elements are well known to the skilled artisan and are comparable to the methods set forth above (i.e., synthesis of the DNA, library screening, and the like).

20

Vector and Host Cell

Preferred vectors for practicing this invention are those which are compatible with bacterial, insect, and mammalian host cells. Such vectors include, by way of illustration, pCRII, pCR3, and pCDNA3 (Invitrogen Company, San Diego, California), pBSII (Stratagene Company, La Jolla, California), pET15b (Novagen, Madison, Wisconsin), pGEX (Pharmacia Biotech, Piscataway, New Jersey), and pEGFP-N2 (Clontech, Palo Alto, California).

After the vector has been constructed and a nucleic acid molecule encoding full length or truncated polypeptide, or an analog thereof, has been inserted into the proper site of the vector, the completed

vector may be inserted into a suitable host cell for amplification or polypeptide expression.

Host cells may be prokaryotic host cells (such as
5 *E. coli*) or eukaryotic host cells (such as yeast,
insect or vertebrate cells). The host cell, when
cultured under suitable nutrient conditions, will
synthesize the polypeptide, which can subsequently be
collected by isolation from the culture medium (if the
10 host cell secretes it into the medium) or directly from
the host cell (if not secreted). For polypeptide
situated in the host cell cytoplasm and/or nucleus, the
host cells are typically first disrupted mechanically
or with detergent to release the intracellular contents
15 into a buffered solution. The polypeptide can then be
collected from this solution. After collection, the
polypeptide can be purified using methods such as
molecular sieve chromatography, affinity
chromatography, and the like.

20

Selection of the host cell for polypeptide
production will depend in part on whether the
polypeptide is to be glycosylated or phosphorylated (in
which case eukaryotic host cells are preferred), and
25 the manner in which the host cell is able to "fold" the
protein into its native tertiary structure (e.g.,
proper orientation of disulfide bridges, etc.) such
that biologically active protein is prepared by the
cell. Even where the host cell does not synthesize the
30 polypeptide in the proper conformation, the polypeptide
may be "folded" after synthesis using appropriate
chemical conditions such as discussed below.

Suitable cells or cell lines may be mammalian
35 cells, such as Chinese hamster ovary cells (CHO) or 3T3
cells. The selection of suitable mammalian host cells

and methods for transformation, culture, amplification, screening and product production and purification are known in the art. Other suitable mammalian cell lines, are the monkey COS-1 and COS-7 cell lines, and the CV-1
5 cell line. Further exemplary mammalian host cells include primate cell lines and rodent cell lines, including transformed cell lines. Normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, as well as primary explants, are also
10 suitable. Candidate cells may be genotypically deficient in the selection gene, or may contain a dominantly acting selection gene. Other suitable mammalian cell lines include, but are not limited to, mouse neuroblastoma N2A cells, HeLa, mouse L-929 cells,
15 3T3 lines derived from Swiss, Balb-c or NIH mice, BHK or HaK hamster cell lines.

Similarly useful as host cells are bacterial cells. For example, the various strains of *E. coli*
20 (e.g., HB101, DH5 α , DH10, and MC1061) are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Pseudomonas spp.*, other *Bacillus spp.*, *Streptomyces spp.*, and the like may also be employed in this method.

25

Many strains of yeast cells known to those skilled in the art are also available as host cells for use with the present invention.

30 Insertion of the vector into the selected host cell (also referred to as "transformation" or "transfection") may be accomplished using known materials or methods such as calcium chloride, electroporation, microinjection, lipofection or the
35 DEAE-dextran method.

Host Cell Culturing

Host cells containing the vector may be cultured using standard media well known to the skilled artisan.

5 The media will usually contain all of the nutrients necessary for the growth and survival of the transformed cells. Suitable media for culturing *E. coli* cells are, for example, Luria Broth (LB) and/or Terrific Broth (TB). Suitable media for culturing

10 eukaryotic cells are RPMI 1640, MEM, DMEM, all of which may be supplemented with serum and/or growth factors as required by the particular cell line being cultured. A suitable medium for the culturing of insect cells is Grace's medium supplemented with yeastolate,

15 lactalbumin hydrolysate and/or fetal calf serum, as necessary.

Typically, an antibiotic or other compound useful for selective growth of the transformed cells is added

20 as a supplement to the growth medium. The compound to be used will be dictated by the selectable marker element present on the plasmid with which the host cell has been transformed or transfected. For example, where the selectable marker element is kanamycin

25 resistance, the compound added to the culture medium will be kanamycin.

The amount of polypeptide produced in the host cell can be evaluated using standard methods known in

30 the art. Such methods include, without limitation, Western blot analysis, SDS-polyacrylamide gel electrophoresis, non-denaturing gel electrophoresis, HPLC separation, immunoprecipitation, and/or activity assays such as DNA binding gel shift assays.

Recovery of Expression Product

Purification of polypeptides according to this invention from solution can be accomplished using a variety of techniques. If the polypeptide has been synthesized such that it contains a tag, it may essentially be purified in a one-step process by passing the solution through an affinity column where the column matrix has a high affinity for the tag or for the polypeptide directly (i.e., a monoclonal antibody specifically recognizing the polypeptide). For example, polyhistidine binds with great affinity and specificity to nickel, thus an affinity column of nickel (such as the Qiagen® nickel columns) can be used for purification. See, for example, Current Protocols in Molecular Biology, Volume 1, Edited by Ausubel et al., John Wiley and Sons, Inc. (1995).

Where the polypeptide is prepared without a tag attached, and no antibodies are available, other well known procedures for purification can be used. Such procedures include, without limitation, ion exchange chromatography, molecular sieve chromatography, HPLC, native gel electrophoresis in combination with gel elution, and preparative isoelectric focusing.

If the polypeptide has been formed with inclusion bodies in the periplasm, the inclusion bodies can often bind to the inner and/or outer cellular membranes and thus will be found primarily in the pellet material after centrifugation. The pellet material can then be treated with a chaotropic agent such as guanidine or urea to release, break apart, and solubilize the inclusion bodies. The polypeptide in its now soluble form can then be analyzed using gel electrophoresis, immunoprecipitation or the like. If it is desired to

isolate the, isolation may be accomplished using standard methods such as those described by Marston et al. in Meth. Enz., Volume 182, pages 264-275 (1990).

5 In those situations where it is preferable to partially or completely isolate the polypeptide, purification can be accomplished using standard methods well known to the skilled artisan. Such methods include, without limitation, separation by
10 electrophoresis followed by electroelution, various types of chromatography (immunoaffinity, molecular sieve, and/or ion exchange), and/or high pressure liquid chromatography. In some cases, it may be preferable to use more than one of these methods for
15 complete purification.

Gene Therapy

 The human DNA molecules provided herein (or
20 corresponding RNAs) may also be used for gene therapy, depending on the biological activity and desired effect. Currently, vectors suitable for gene therapy (such as retroviral or adenoviral vectors modified for gene therapy purposes and of purity and pharmaceutical
25 acceptability) may be administered for delivery into the lung, for example. Such vectors may incorporate nucleic acid encoding the present polypeptides for expression in a desired location. Gene therapy may involve more than one gene for a desired protein or
30 different desired proteins.

 Alternatively, one may use no vector so as to facilitate relatively stable presence in the host. For example, homologous recombination of a DNA as provided
35 herein or of a suitable transcription or translation control region may facilitate integration into or

expression from a host genome. (This may be performed for production purposes as well, for example, United States Patent No. 5,272,071, issued December 21, 1993, and PCT application WO 91/09955, published July 11, 1991). The nucleic acid may be placed within a pharmaceutically acceptable carrier to facilitate cellular uptake, such as a lipid solution carrier (e.g., a charged lipid), a liposome, or polypeptide carrier (e.g., polylysine).

10

Thus, the present invention provides for a population of cells expressing the polypeptides of this invention. Such cells may be suitable for transplantation or implantation into an individual for therapeutic purposes. For example, one may prepare a population of cells to overexpress the polypeptide. One may then implant such cells into an individual. Such cells may be, for example, liver cells, bone marrow cells, or cells derived from umbilical cord. Alternatively, one may wish to use overexpressing circulating cells such as blood progenitor cells, T cells or other blood cells. Human cells may be used. Cells may be in the form of tissue. Such cells may be cultured prior to transplantation or implantation. In situ expression may be accomplished by, for example, by altering the regulatory mechanism for expression of the polypeptide, such as by using homologous recombination techniques as referred to above. Thus, provided is a population of host cells modified so that expression of endogenous polypeptide DNA is enhanced.

The cells to be transferred to the recipient may be cultured using one or more factors affecting the growth or proliferation of such cells, if appropriate. Hematopoietic factors may be used in culturing hematopoietic cells. Such factors include G-CSF, EPO,

35

MGDF, SCF, Flt-3 ligand, interleukins (e.g., IL-1 to IL-13), GM-CSF, LIF, and analogs and derivatives thereof as available to one skilled in the art.

- 5 There may be a co-gene therapy involving the transplantation of cells expressing more than one desired protein.

10 For gene therapy dosages, one will generally use between one copy and several thousand copies of the present nucleic acid per cell, depending on the vector, the expression system, the age, weight and condition of the recipient, and other factors which will be apparent to those skilled in the art. The cellular delivery of
15 the polypeptide(s) may be designed to last for a selected period of time, such as a period of days, weeks, months or years. At the end of the effective time period, the recipient of the transformed cells may receive another "dose" (e.g., transplantation of
20 cells). Cells may be selected for their lifespan, their time period of expression of the desired polypeptide, or their ability to be reisolated from an individual (i.e., for blood cells, leukaphoresis may be used to retrieve transformed cells using markers
25 present on the cell surface). Vectors may be similarly designed using, for example, viruses which have a known period of expression of DNAs contained therein.

30 The desired cells or vectors may be stored using techniques, such as freezing, available to those in the art.

35 Thus, the present invention also contemplates a method for administering the polypeptide to an individual, wherein the source of the polypeptide is selected from (i) a population of cells expressing the

polypeptide and (ii) a population of vectors expressing the polypeptide. Such vectors may be virus vectors capable of infecting human cells. The cells may be selected from among tissue or individual cells. The individual cells may be selected from among adipocytes, fibroblasts, bone marrow cells, peripheral blood progenitor cells, red blood cells, and white blood cells, including T cells and nerve cells.

10 Polypeptide Derivatives

One may modify the polypeptides of this invention (including fragments and analogs), prepared as described above, to create a fusion molecule with another peptide sequence. For example, if one desired to "tag" the polypeptide with an immunogenic peptide, one could construct a DNA which would result in such fusion product. The tag may be at the N-terminus or the C-terminus. An example is a "FLAG-tag" version of the polypeptide. This type of "tagging" is useful to bind the polypeptide using reagents, such as antibodies, which are selective for the tag. Such binding may be for detection of the location or amount of polypeptide, or for polypeptide capturing processes where, for example, an affinity column is used to bind the tag, and thus the desired polypeptide. Other types of detectable labels, such as radioisotopes, light-emitting (e.g., fluorescent or phosphorescent compounds), enzymatically cleavable, detectable antibody (or modification thereof), or other substances may be used for such labeling of the present polypeptides.

For human therapeutic purposes, it may also be advantageous to derivatize the polypeptides described above by the attachment of one or more other chemical

moieties to the polypeptide moiety. Such chemical moieties may be selected from among various water soluble polymers. The polymer should be water soluble so that the polypeptide to which it is attached is miscible in an aqueous environment, such as a physiological environment. The water soluble polymer may be selected from the group consisting of, for example, polyethylene glycol, copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random or non-random copolymers (see further below regarding fusion molecules), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols, polystyrenemaleate and polyvinyl alcohol. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water.

Fusion polypeptides in accordance with this invention may be prepared by attaching polyamino acids to the polypeptide. For example, the polyamino acid may be a carrier protein which serves to increase the circulation half life of the polypeptide. The polyamino acid should be one which does not create a neutralizing antigenic response, or other adverse response, if the derivative is intended for *in vivo* therapeutic use. The polyamino acid may be selected from the group consisting of serum album (such as human serum albumin), an antibody or portion thereof (such as an antibody constant region, sometimes called "F_C") or other polyamino acids. The location of attachment of the polyamino acid may be at the N-terminus of the

polypeptide moiety, or other place, and also may be connected by a chemical "linker" moiety to the polypeptide.

5 The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 2 kilodaltons (kDa) and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the
10 stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on
15 biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol on a therapeutic protein).

 The number of polymer molecules so attached may
20 vary, and one skilled in the art will be able to ascertain the effect on function. One may mono-derivatize, or may provide for a di-, tri-, tetra- or some combination of derivatization, with the same or different chemical moieties (e.g., polymers, such as
25 different weights of polyethylene glycols). The proportion of polymer molecules to polypeptide molecules will vary, as will their concentrations in the reaction mixture. In general, the optimum ratio (in terms of efficiency of reaction in that there is no
30 excess unreacted polypeptide or polymer) will be determined by factors such as the desired degree of derivatization (e.g., mono, di-, tri-, etc.), the molecular weight of the polymer selected, whether the polymer is branched or unbranched, and the reaction
35 conditions.

The chemical moieties should be attached to the polypeptide with consideration of effects on functional or antigenic domains of the polypeptide. There are a number of attachment methods available to those skilled
5 in the art. See, for example, EP 0 401 384 (coupling PEG to G-CSF), and Malik et al., Experimental Hematology, Volume 20, pages 1028-1035 (1992) (reporting the pegylation of GM-CSF using tresyl chloride). By way of illustration, polyethylene glycol
10 may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule (or other chemical moiety) may be bound. The amino acid residues having a free
15 amino group may include lysine residues and the N-terminal amino acid residue. Those having a free carboxyl group may include aspartic acid residues, glutamic acid residues, and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a
20 reactive group for attaching the polyethylene glycol molecule(s) (or other chemical moiety). Preferred for therapeutic manufacturing purposes is attachment at an amino group, such as at the N-terminus or to a lysine group. Attachment at residues important for receptor
25 binding should be avoided if receptor binding is desired.

One may specifically desire N-terminally chemically modified derivatives. Using polyethylene
30 glycol as an illustration, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to polypeptide molecules in the reaction mixture, the type of pegylation
35 reaction to be performed, and the method of obtaining the selected N-terminally pegylated polypeptide. The

method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated polypeptide molecules. Selective N-terminal chemical modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. See PCT application WO 96/11953, published April 25, 1996. Under the appropriate reaction conditions, substantially selective derivatization of the polypeptide at the N-terminus with a carbonyl group containing polymer is achieved. For example, one may selectively N-terminally pegylate the polypeptide by performing the reaction at a pH which allows one to take advantage of the pK_a differences between the ϵ -amino group of the lysine residues and that of the α -amino group of the N-terminal residue of the polypeptide. By such selective derivatization, attachment of a polymer to a polypeptide is controlled: the conjugation with the polymer takes place predominantly at the N-terminus of the polypeptide and no significant modification of other reactive groups, such as lysine side chain amino groups, occurs. Using reductive alkylation, the polymer may be of the type described above, and should have a single reactive aldehyde for coupling to the polypeptide. Polyethylene glycol propionaldehyde, containing a single reactive aldehyde, may be used.

In general, an N-terminally chemically modified derivative will be preferred over other forms of chemical modification for ease in production of a therapeutic. N-terminal chemical modification ensures

a homogenous product as characterization of the product is simplified relative to di-, tri- or other multi-derivatized products. The use of the above reductive alkylation process for preparation of an N-terminally
5 chemically modified product is preferred for ease in commercial manufacturing.

Chemically modified derivatives in accordance with this invention may be further formulated for intra-
10 arterial, intraperitoneal, intramuscular, subcutaneous, intravenous, oral, nasal, pulmonary, topical or other routes of administration, again depending on the biological activity of the polypeptide and the desired therapeutic effect. Chemical modification of
15 biologically active proteins has been found to provide additional advantages under certain circumstances, such as increasing the stability and circulation time of the therapeutic protein and decreasing the immunogenicity. See, for example, United States Patent No. 4,179,337,
20 issued December 18, 1979 (Davis et al.), and Abuchowski et al., "Enzymes as Drugs", Edited by Holcerberg and Roberts, pages 367-383 (1981). A review describing protein modification and fusion proteins is Francis, Focus on Growth Factors, Volume 3, pages 4-10,
25 published by Mediscript, Mountview Court, Friern Barnet Lane, London, England (1992). Preferably, for therapeutic use of the end-product preparation, the chemical moiety for derivatization will be pharmaceutically acceptable.

30

Therapeutic Compositions

Another aspect of the present invention involves the use of the polypeptide of SEQ ID NO: 4 and analogs
35 and derivatives thereof in pharmaceutical compositions and in methods for the manufacture of medicaments for

use in humans. Such compositions may be for administration by injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, encompassed within the invention are

5 pharmaceutical compositions comprising effective amounts of polypeptide or derivative products of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. By "effective amount" is

10 meant an amount sufficient to produce a measurable biological effect. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80,

15 Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as

20 polylactic acid, polyglycolic acid, etc., or into liposomes. See, for example, PCT application WO 96/29989, Collins et al., published October 3, 1996. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the

25 circulation. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the present proteins and derivatives. See, for example, Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing

30 Co., Easton, Pennsylvania, pages 1435-1712 (1990). The compositions may be prepared in liquid form, or as a dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

Also contemplated are oral dosage forms of the above derivatized polypeptides. Proteins may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated for the present purposes is the attachment of at least one moiety to the polypeptide molecule itself, where this moiety permits (a) inhibition of proteolysis and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the protein and increase in circulation time in the body. See PCT application WO 95/21629 (Habberfield, "Oral Delivery of Chemically Modified Proteins"), published August 17, 1995, and United States Patent No. 5,574,018, issued November 12, 1996 (Habberfield et al., "Conjugates of Vitamin B12 and Proteins"), issued November 12, 1996.

Also contemplated herein is pulmonary delivery of such polypeptides and derivatives. The polypeptide or polypeptide analog or derivative is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. For illustration, see PCT application WO 94/20069, Niven et al., "Pulmonary Administration of Granulocyte Colony Stimulating Factor", published September 15, 1994.

Nasal delivery of the polypeptide (or analog or derivative) may also be possible. Nasal delivery allows the passage of the polypeptide (or derivative) to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with

absorption enhancing agents, such as dextran or cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

5 If desired, the polypeptides of this invention may also be administered systemically in a sustained release formulation or preparation. Suitable examples of sustained release preparations include semipermeable polymer matrices in the form of shaped articles, for
10 example, films or microcapsules. Sustained release matrices include polyesters, hydrogels, polylactides (United States Patent No. 3,773,919, issued November 20, 1973), copolymers of L-glutamic acid and gamma ethyl-L-glutamine (Sidman et al, Biopolymers, Volume
15 22, pages 547-556, 1983), poly (2-hydroxyethyl-methacrylate) (Langer et al., J. Biomed. Mater. Res., Volume 15, pages 167-277, 1981, and Langer, Chem. Tech., Volume 12, pages 98-105, 1982), ethylene vinyl acetate (Langer et al., above), or poly-D(-)-3-
20 hydroxybutyric acid. Sustained-release compositions also may include liposomes, which can be prepared by any of several methods known in the art; see, for example, Epstein et al., Proceedings of the National Academy of Sciences USA, Volume 82, pages 3688-3692
25 (1985), and Hwang et al., Proceedings of the National Academy of Sciences USA, Volume 77, pages 4030-4034 (1980).

Typically, the polypeptide will be in highly
30 purified form, and the composition will normally be presterilized for use, such as by filtration through sterile filtration membranes.

The amount of polypeptide that will be effective
35 in vivo will depend on the nature of the application. One skilled in the art will be able to ascertain

effective dosages by administration and observing the desired therapeutic effect. Particular effective does within this range will depend on the particular disorder or condition being treated, as well as the age and general health of the recipient, and can be determined by standard clinical procedures. Where possible, it will be desirable to determine the dose-response curve of the pharmaceutical composition first *in vitro*, as in bioassay systems, and then in useful animal model systems *in vivo* prior to testing in humans. The skilled practitioner, considering the therapeutic context, type of disorder under treatment, and other applicable factors, will be able to ascertain proper dosing without undue effort. Typically, a practitioner will administer the polypeptide composition until a dosage is reached that achieves the desired effect. The composition may be administered as a single dose, or as two or more doses (which may or may not contain the same amount of polypeptide) over time, or on a continuous basis.

Diagnostic Materials and Methods

Nucleic acid products of the invention may be labeled with detectable markers (such as radiolabels and non-isotopic labels such as biotin) and employed in hybridization processes to locate the gene position and/or the position of any related gene family in a chromosomal map. They may also be used for identifying gene disorders at the DNA level and used as gene markers for identifying neighboring genes and their disorders. Such nucleic acid sequences may be used for detection or measurement of mRNA level from a biological sample. Contemplated herein are kits containing such labeled materials.

The polypeptides and/or nucleic acids provided herein may be embodied as part of a kit or article of manufacture. An example is an article of manufacture comprising a packaging material and one or more preparations of the presently provided compositions. Such packaging material will comprise a label indicating that the polypeptide or nucleic acid preparation is useful for detecting and/or quantifying the amount of polypeptide in a biological sample, or defects in a biological sample. As such, the kit may optionally include materials to carry out such testing, such as reagents useful for performing DNA or RNA hybridization analysis, or PCR analysis on blood, urine, or tissue samples.

A further aspect of the invention is binding molecules, such as polyclonal antibodies, or preferably, monoclonal antibodies selectively binding the polypeptides of this invention. The hybridoma technique described originally by Kohler and Milstein in the European Journal of Immunology, Volume 6, pages 511-519 (1976), has been widely applied to produce hybrid cell lines that secrete high levels of monoclonal antibodies against many specific antigens. Recombinant antibodies may also be prepared; see Huse et al., Science, Volume 246, at page 1275 (1989). Such recombinant antibodies may be further modified, such as by modification of complementarity determining regions to increase or alter affinity, or "humanizing" such antibodies, and incorporated into a kit for diagnostic purposes. A diagnostic kit may be employed to determine the location and/or amount of the polypeptide of this invention in an individual. Diagnostic kits may also be used to determine if an individual has receptors which the polypeptide, or those which, to

varying degrees, have reduced binding capacity or ability. Such antibodies may be prepared using immunogenic portions of the polypeptide. Such selective binding molecules may themselves be
5 alternatives to the polypeptide, and may be formulated for pharmaceutical use.

Such polypeptides and/or nucleic acids may be used for tissue distribution assays (for example, as
10 provided in the working example below) or for other assays to determine the expression pattern of the polypeptide.

The biological function of the polypeptide(s) of
15 this invention can be studied *in vivo* by disrupting expression of the corresponding gene in non-human animals such as mice, such that the level of expression of this gene is significantly decreased or completely abolished (so-called "knock out" animals). Such
20 animals may be prepared with the use of techniques and methods described in United States Patent No. 5,557,032, issued September 17, 1996, for example. Additionally, or alternatively, mice can be prepared in which the gene for the polypeptide is overexpressed
25 ("transgenic" animals) in order to evaluate the effects of the overexpression. Suitable methods for the preparation of such transgenic animals are described in United States Patent No. 5,489,743, issued February 6, 1996, and in PCT application WO 94/28122, published
30 December 8, 1994. Useful transgenic animals will be those which display a detectable phenotype associated with expression of the polypeptide.

Another potential use of the present polypeptides
35 is in assays and methods for the identification of a receptor or receptors which bind to, and are activated

by, the polypeptides. This can be accomplished, for instance, by contacting a recombinant host cell (bacterial, yeast, etc.) expressing the polypeptide of this invention ("ligand") on the surface with a
5 receptor to be identified under conditions which permit binding or receptor activation, and detecting the occurrence of any such binding or activation. Such "ligand-receptor" interactions can take place cell to cell, since the membrane-bound polypeptide of this
10 invention is believed to interact through contact with the receptor on an adjacent cell. Thus, the assay can involve recombinant expression of the "ligand" and the "receptor" on the surface of separate host cells, which are then brought into proximity or direct contact to
15 determine whether ligand-receptor binding or receptor activation occurs. The binding or activation event would then be detected by standard means, such as by measurement of the change in an analytically detectable label which has been attached to either the ligand or
20 receptor, or by measurement of autophosphorylation of the receptor (if the latter is capable of phosphorylation upon activation).

Alternatively, the assay can be carried out using
25 a "soluble" version of the polypeptide of the invention, consisting of the extracellular domain (with or without the signal peptide region) which has been recombinantly expressed and harvested from the host. The soluble polypeptide can be employed alone, or in
30 derivatized form, e.g., an "Fc fusion" product such as described above (and exemplified below). The soluble polypeptide or derivative is then brought into proximity or contact with a substrate to which the receptor to be identified has been bound, and the
35 binding or activation event is detected in the same manner as described above. The procedure can also be

conducted in reverse, i.e., with the receptor to be identified being bound to a suitable substrate and the unbound soluble polypeptide or derivative being contacted therewith, etc.

5

The purified polypeptide of this invention will also be useful for structural studies as a means for the rational design of novel drugs affecting the *in vivo* function and activity of the polypeptide. For instance, the recombinant protein may be used to derive the structure of the protein through X-ray crystallography, NMR or modeling from published structures of related proteins. Knowledge of the structure will foster an understanding of how the polypeptide binds, and can lead to the design or discovery of compounds which can either block or mimic the activity of the polypeptide, depending on what is desired.

20

Description of Specific Embodiments

The invention is described in further detail with regard to the following working examples, which are included for purposes of illustration only and are not intended to be limiting.

25

Example 1

Construction of cDNA Library

30

Normal white adipose tissue was collected from CD-1 mice, and total mRNA was isolated using an RNeasy Maxi[®] kit (Qiagen, Santa Clara, California) in accordance with the manufacturer's instructions. The proportion of RNA containing a polyA sequence was

35

subsequently isolated (Oligotex kit, Qiagen, Santa Clara, California) as per instructions except for the omission of the DNase step.

5 A cDNA library was constructed with this mRNA using the Super Script[®] Plasmid System (Gibco BRL, Gaithersburg, Maryland). The manufacturer's protocol was followed except that a custom random
10 oligonucleotide primer containing a NotI restriction site was substituted for the first strand synthesis step and a PCR Clean up kit (Qiagen, Santa Clara, California) was used to purify the products of the second strand synthesis and SalI adapter ligation steps. The cDNA was size-fractionated using agarose
15 gel electrophoresis (Maniatis, Molecular Cloning, CSH Press, 1991), and the 200-800 base pair products were excised. These fragments were then ligated into shuttle vector pYYA-41L which had been previously digested with the enzymes XhoI and NotI. Vector pYYA-
20 41L was deposited with the American Type Culture Collection, Manassas, Virginia, on February 13, 1998, under accession number 209636.

 Vector pYYA-41L contains the ampicillin resistance
25 gene and the Trp1 gene for selection in *E. coli* and *S. cerevisiae*, respectively. In addition, the vector contains a yeast promoter upstream from the yeast amylase gene in which the signal peptide sequence has been deleted. The vector is constructed such that
30 insertion of a functional signal sequence into the XhoI-NotI restriction sites results in secretion of the amylase gene product outside the yeast cell wall. The ligated vector was amplified by transformation into

E. coli (DH10b, Gibco BRL, Gaithersburg, Maryland), and then isolated using a Qiagen plasmid purification kit (Qiagen, Santa Clara, California).

5 The resulting DNA was used to transform YPH499 yeast using lithium acetate; for reference, see Gietz et al., *Nucleic Acids Research*, Volume 20, page 1425 (1992). The transformed yeast cells were then plated onto agar containing starch azure (Sigma, St. Louis, 10 Missouri) and lacking tryptophan. Following incubation at 30°C, yeast colonies surrounded by a clearing of the azure plate (indicating secretion of the amylase gene) were picked. Individual yeast colonies were isolated by re-streaking on plates and grown in liquid culture, 15 and the vector DNA was then isolated using a Qiagen plasmid purification kit (Qiagen, Santa Clara, California). The DNA sequences of the vector inserts were determined by PCR amplification (Perkin Elmer, Sunnyvale, California) using vector specific primers, 20 purification of the amplified DNA (Qiagen, Santa Clara, California), and automated DNA sequencing (Perkin Elmer/Applied Biosystems, Foster City, California).

25 The resulting DNA sequences and predicted protein sequences were searched against available public databases containing nucleotide and protein sequences. One sequence (SEQ ID NO: 41), composed of 402 base pairs, showed significant homology to previously isolated members of the Delta gene family.

Example 2Cloning of the Murine Gene

5 Murine adipose cDNAs longer than eight hundred base pairs were ligated to adaptor primers using a Marathon[®] cDNA amplification kit (Clontech, Palo Alto, California) and the manufacturer's protocol. The final cDNA products were purified from unligated adaptor
10 primers (PCR Clean-up kit, Qiagen, Chatsworth, California) and then used as templates for subsequent rapid amplification of cDNA ends (RACE) reactions using polymerase chain reaction (PCR).

15 For the 3' RACE reaction, PCR was performed on the cDNA templates using Advantage[®] PCR kit components (Clontech, Palo Alto, California) and the following primers:

20 TGCTGTGGGTAAGATTTGGCGAACA (SEQ ID NO: 42) and
CCATCCTAATACGACTCACTATAGGGC (SEQ ID NO: 43).

Following denaturation (94°C for one minute), the amplification procedure was conducted as follows: five
25 cycles at 94°C for five seconds and at 72°C for four minutes; five cycles at 94°C for five seconds and at 70°C for four minutes; and twenty five cycles at 94°C for five seconds and at 68°C for four minutes. All reactions were performed on a Perkin Elmer 2400 PCR
30 machine (Sunnyvale, California).

The reaction mixture was electrophoresed on a 1% agarose gel, and a single band migrating at approximately 3 kilobases was excised and purified
35 through a Genelute[®] column (Supelco, Bellefonte,

Pennsylvania), then ligated into a pCR-Blunt plasmid (Invitrogen, Carlsbad, California). Bacterial host cells were then transformed with this plasmid and grown overnight. The plasmid DNA was isolated from the
5 bacteria host cells using the Qiagen miniprep protocol and digested with EcoRI and NotI to confirm the presence and size of the inserts. A clone containing an insert of approximately 3 kilobases (SEQ ID NO: 44) was sequenced and found to contain a novel cDNA
10 encoding murine polypeptide. This DNA sequence was used to design primers for a 5' RACE reaction.

For the 5' RACE reaction, PCR was performed on the cDNA templates using Advantage[®] PCR kit components
15 (Clontech, Palo Alto, California) together with the following primers:

GGTGAGTCCGCACAGGTCAAGGTAC (SEQ ID NO: 45) and
CCATCCTAATACGACTCACTATAGGGC (SEQ ID NO: 43).

20 Following an initial denaturation step (94°C for one minute), amplification was carried out as follows: five cycles at 94°C for five seconds and at 72°C for four minutes; five cycles at 94°C for five seconds and
25 at 70°C for four minutes; and twenty-five cycles at 94°C for five seconds and at 68°C for four minutes.

The reaction mixture was electrophoresed on a 1% agarose gel, and a single band migrating at
30 approximately 1.5 kilobases was excised, purified as above, and reamplified using the Advantage[®] PCR kit components with the following oligonucleotides:

GACAGGGGTTGCTGGCACACTTGTT (SEQ ID NO: 46) and
35 CCATCCTAATACGACTCACTATAGGGC (SEQ ID NO: 43).

Following denaturation (94°C for one minute), the template was amplified over thirty-five cycles at 94°C for ten seconds and at 72°C for two and one-half minutes.

The reaction mixture was electrophoresed on a 1% agarose gel, and a single band migrating at approximately 1.7 kilobases was excised and purified through a Genelute® column and then ligated into the pCR2.1 plasmid (Invitrogen, Carlsbad, California). Bacterial host cells were transformed with this plasmid and grown overnight. The plasmid DNA was isolated from the bacteria host cells using the Qiagen miniprep protocol, then digested with EcoRI to confirm the presence and size of the inserts. Three clones, containing an insert of approximately 1.5 kilobases, were sequenced and shown to contain additional 5' murine cDNA sequence composed of 982 base pairs (SEQ ID NO: 47).

The sequence of this 5' RACE clone (SEQ ID NO: 47) was merged with the sequence of the 3' RACE clone (SEQ ID NO: 44) to give the full length murine cDNA open reading frame sequence (Figure 1A-1B, and SEQ ID NO: 1).

To generate a full length murine cDNA clone of SEQ ID NO: 1 (above), PCR was performed on the murine white adipose template from the RACE reactions using the Advantage® PCR kit components and the following oligonucleotides:

AGCCACCATGACGCCTGCGTCCCG (SEQ ID NO: 48) and
TCTATTATACCTCTGTGGCAATCAC (SEQ ID NO: 49).

Following denaturation (94°C for one minute), the template was amplified with ten cycles of heating at 94°C for ten seconds, 55°C for ten seconds, and 72°C for two and one-half minutes; followed by twenty five cycles of heating at 94°C for ten seconds, 62°C for ten seconds and 72°C for two and one-half minutes.

The reaction mixture was electrophoresed on a 1% agarose gel and a single band migrating at approximately 2.2 kilobases was excised and purified through a Genelute® column and ligated into a pCR2.1 plasmid (Invitrogen, Carlsbad, California). Bacterial host cells were transformed with this plasmid and grown overnight. The plasmid DNA was then isolated from the bacteria host cells using the Qiagen miniprep protocol and digested with EcoRI to confirm the presence and size of the inserts. Three clones, containing an insert of approximately 2.2 kilobases, were sequenced and one clone was shown to contain the complete murine cDNA (SEQ ID NO: 1, Figure 1A-1B). This cDNA molecule encodes a murine polypeptide (herein termed "D114") having the predicted amino acid sequence of Figure 2 (SEQ ID NO: 2).

Example 3

Identification of the Human Gene

The murine DNA sequence (SEQ ID NO: 1) was searched against the GenBank database (Wisconsin Package Version 9.1, Genetics Computer Group, Madison, Wisconsin), and a 409-base pair sequence (SEQ ID NO: 50) from a human brain cDNA library was found that had 81.37% sequence identity to the murine polypeptide.

The following oligonucleotides were designed from areas of high homology between SEQ ID NO: 50 and SEQ ID NO: 1:

- 5 AAGAAGGAGCTGGAAGTGGACTGTG (SEQ ID NO: 51) and
 ATCAAACACACAGACTGGTACATGG (SEQ ID NO: 52).

10 These oligonucleotides were used to amplify a
Marathon human brain cDNA library (Clontech, Palo Alto,
California) using the Advantage[®] PCR kit components
(Clontech, Palo Alto, California). Following an
initial denaturation step (94°C for one minute),
amplification was carried out as follows: five cycles
at 94°C for five seconds and 72°C for two and one-half
15 minutes; five cycles at 94°C for five seconds and 70°C
for two and one-half minutes; and twenty-five cycles at
94°C for five seconds and 68°C for two and one-half
minutes.

20 The reaction mixture was electrophoresed on a 1%
agarose gel and a single band migrating at
approximately 245 base pairs was excised, purified
through a Genelute[®] column, and reamplified under the
same reaction conditions.

25

 The resulting 245-base pair product was purified
with a PCR Clean-up kit (Qiagen, Chatsworth,
California) and labeled with α -³²P-dCTP (RediVue,
Amersham, Arlington Heights, Illinois), using a
30 RediPrime[®] random primed reaction kit (Amersham,
Arlington Heights, Illinois). Unincorporated
radioactivity was excluded by size exclusion
chromatography (5Prime-3Prime, Boulder, Colorado). A
human fat cell 5' Stretch Plus cDNA lambda gt10 library

(Clontech, Palo Alto, California) was then screened for the human gene with this α -³²P-dCTP labeled cDNA probe. Seventy-two filters were hybridized with the labeled cDNA probe in 100 milliliters of RapidHyb[®] buffer (Amersham, Arlington Heights, Illinois) for approximately sixteen hours at 65°C. The filters were then washed twice in 2X SSC (0.3 M sodium chloride/0.3 M sodium citrate) with 0.2% SDS at room temperature for thirty minutes, followed by two washes in 0.2X SSC with 0.2% SDS at 65°C for thirty minutes. The filters were placed in autoradiography cassettes and exposed to Hyperfilm (Amersham, Arlington Heights, Illinois) at -80°C overnight. The film was developed, and one clone was identified which hybridized to the probe.

This phage clone was plaque purified using standard methods, isolated using the Wizard Lambda Prep DNA Purification System (Promega, Madison, Wisconsin), and sequenced. The sequence (SEQ ID NO: 53) showed that this clone contained approximately 215 base pairs of 5' untranslated region and 1980 base pairs of the coding region for the human polypeptide. The clone also lacked the last 85 base pairs of the coding region.

To amplify the remaining 3' end of the human gene, the oligonucleotide primers shown below were designed from the clone of SEQ ID NO: 50 downstream of the termination codon and from the sequence for the above mentioned human phage clone (SEQ ID NO: 53).

ACCTGATTCCTGCCGCCAGCT (SEQ ID NO: 54) and
GATGTCCCAGGTAGGCTCCTGC (SEQ ID NO: 55).

These oligonucleotides were used to amplify a Marathon human lung cDNA library (Clontech, Palo Alto,

California) using the pfu polymerase (Stratagene, La Jolla, California). Following denaturation at 94°C for one minute, amplification was carried out over thirty cycles at 94°C for fifteen seconds, 68°C for fifteen
5 seconds, and 74°C for one minute.

The reaction mixture was electrophoresed on a 1% agarose gel and a single band migrating at approximately 300 base pairs was excised and purified
10 through a Genelute® column and ligated into the pCR-Blunt plasmid (Invitrogen, Carlsbad, California). Bacterial host cells were then transformed with this plasmid and grown overnight. The plasmid DNA was
15 miniprep protocol and digested with EcoRI and SpeI to confirm the presence and size of the inserts. Three clones containing an insert of approximately 300 base pairs were sequenced and compared to SEQ ID NO: 50 and
20 coverage sequencing of this clone revealed that it had the sequence of SEQ ID NO: 56.

This sequence (SEQ ID NO: 56) and the sequence of SEQ ID NO: 53 were merged using Sequencer software
25 (Gene Codes, Ann Arbor, Michigan) into the full length human open reading frame sequence (Figure 3A-3B, SEQ ID NO: 3). This DNA sequence encodes a human polypeptide having the predicted amino acid sequence of Figure 4
(SEQ ID NO: 4).

Example 4Expression of the Murine Gene

5 To assess the gene expression pattern of the murine polypeptide, RT-PCR was performed on ten nanograms of mRNA from various murine tissues using the GeneAmp EZ *rTth* RNA PCR Kit (Perkin-Elmer, Norwalk, Connecticut) and the following oligonucleotide primers:

10

AACCTGGACGGCAGATG (SEQ ID NO: 57) and
AGATTTGGCGAACAGACGA (SEQ ID NO: 58).

15 Following first strand cDNA synthesis at 60°C for thirty minutes and denaturation at 94°C for two minutes, amplification was carried out using thirty cycles at 94°C for fifteen seconds, followed by 66°C for one minute. Reactions were performed with a Perkin Elmer 2400 PCR machine. The reaction mixtures were
20 then purified with a PCR Clean-up Kit (Qiagen, Chatsworth, California), an aliquot of each was run on a 1% agarose gel, and an expected 275-base pair fragment was observed in most tissues. The highest level of expression was seen in the lung, followed by
25 white and brown adipose tissue. Other tissues expressing the murine polypeptide at lower levels of expression were the adrenal gland, spleen, brain, eye, kidney, and the liver. Skin and skeletal muscle were negative at this level of examination.

30

 These same oligonucleotide primers were used to amplify a region from the clone of SEQ ID NO: 41 using a PCR Core Kit (Boehringer Mannheim, Indianapolis, Indiana) as a probe. Following an initial denaturation
35 step (94°C for one minute), the amplification procedure

consisted of thirty cycles at 94°C for fifteen seconds followed by 66°C for one minute. An aliquot of the reaction mixture was electrophoresed on a 1% agarose gel and a single band migrating at approximately 275
5 base pairs was observed. The remainder of the reaction mixture was purified with a PCR Clean-up kit (Qiagen, Chatsworth, California) and labeled with α -³²P-dCTP (RediVue®, Amersham, Arlington Heights, Illinois) using a RediPrime® random primed reaction kit (Amersham,
10 Arlington Heights, Illinois). Unincorporated radioactivity was excluded by size exclusion chromatography (5Prime-3Prime, Boulder, Colorado).

This murine probe was used to screen Northern
15 blots containing two micrograms per lane of polyA+ RNA from various murine tissues (Clontech, Palo Alto, California) in ten milliliters of RapidHyb buffer (Amersham, Arlington Heights, Illinois. Screening was carried out for approximately one hour at a temperature
20 of 65°C. The filters were then washed twice in 2X SSC with 0.2% SDS at room temperature for thirty minutes, followed by two washes in 0.2X SSC with 0.2% SDS at 65°C for thirty minutes. Blots were then exposed to Phosphor Cassettes (Molecular Dynamics, Sunnyvale,
25 California) overnight and developed with a Molecular Dynamics Storm 820 system.

Northern blot analysis showed the level of murine gene expression was highest in the lung, followed by
30 heart, kidney, skeletal muscle and brain. Transcripts were barely detectable in spleen and testis tissues, and hybridization to GAPDH showed little RNA in these lanes.

In Situ Hybridization of the Murine Gene

A panel of normal embryonic (E10.5 through E18.5) and adult mouse tissues were fixed in 4% paraformaldehyde, then embedded in paraffin and sectioned at five micrometers. Prior to *in situ* hybridization, tissues were permeabilized with 0.2M HCL, followed by digestion with Proteinase K and acetylation with triethanolamine and acetic anhydride. Sections were hybridized overnight at 55°C with a 2058-base pair ³³P-labeled riboprobe corresponding to nucleotides 1 to 2058 of the mouse sequence, then subjected to a high stringency wash in 0.1X SSC at 55°C. Slides were dipped in a Kodak NTB2 emulsion (Eastman Kodak, Rochester, New York), exposed at 4°C for two to three weeks, developed, and then counterstained with hematoxylin/eosin. Sections were examined with standard (brightfield) and darkfield illumination to allow simultaneous evaluation of tissue morphology and hybridization signal. Hematoxylin/eosin differentially stained nuclei and cytoplasm and allowed, under brightfield illumination, visualization of cellular morphology and identification of cell types expressing the gene of interest. Emulsion autoradiography allowed microscopic evaluation of the hybridization signal (from the hybridized radiolabeled probe) under darkfield illumination, in which developed silver grains appeared as bright dots on a dark background.

The tissues examined in this manner included:
GI (esophagus, stomach, duodenum, jejunum, ileum, proximal and distal colon), brain (one sagittal, two coronal sections), liver, lung, heart, spleen, thymus,

lymph nodes, kidney, adrenal, bladder, pancreas, salivary gland, male and female reproductive organs (ovary, oviduct and uterus in the female; testis, epididymis, prostate, seminal vesicle and vas deferens in the male), BAT and WAT (subcutaneous, peri-renal, peri-ovarian or epididymal), bone (femur), skin, breast, and skeletal muscle.

The results for tissues from an adult mouse are shown in Figures 5 and 6. The results from mouse embryos are shown in Figure 7. Brightfield illumination is shown on the top panel and darkfield illumination is shown on the bottom panel of each paired set of photographs. Figs. 5A and 5B: lung. Figs. 5C and 5D: liver. Figs. 5E and 5F: brain. Figs. 5G and 5H: choroid plexus. Figs. 5I and 5J: kidney. Figs. 5K and 5L: adrenal gland. Figs. 5M and 5N: spleen. Figs. 5O and 5P: thymus gland. Figs. 6A and 6B: white adipose tissue. Figs. 6C and 6D: brown adipose tissue. Figs. 6E and 6F: skeletal muscle. Figs. 6G and 6H: skin. Figs. 6I and 6J: duodenum. Figs. 6K and 6L: pancreas. Figs. 6M and 6N: ovary. Figs. 6O and 6P: testis. Figs. 7A and 7B: E10.5 mouse embryo. Figs. 7C and 7D: E11.5 mouse embryo. ("E10.5" and "E11.5" indicate day of embryo development; "H" and "L" indicate heart and lung, respectively).

As shown in these photographs, the probe produced a clear signal, with little or no background signal, in tissue sections from both embryo and adult mice. At all of the embryonic stages examined and in all of the adult tissues, signal was restricted to cells with an endothelial-type morphology in blood vessels or capillaries. Signal in the heart was confined to the microvasculature (see Figure 7).

Example 6Preparation of Fc Fusion Derivative

5 An "Fc" fusion derivative of the polypeptide of this invention (using the murine species as an example) and a polyamino acid can be prepared as follows:

10 Most of the extracellular region of murine Delta4 (nucleotides 1-1587 of SEQ ID NO: 1 and Figure 1A-1B) is amplified with the following oligos to add a Spe I site on the 5' end and a Not I site at the 3' end.

GAACTAGTCCACCATGACGCCTGCGTCCCG (SEQ ID NO: 59)

15

TCGCGGCCGCGGGGAAGCTGGGTGGCAA (SEQ ID NO: 60)

Following an initial denaturation step of 94°C for one minute, amplification is carried out over thirty cycles
20 at 94°C for fifteen seconds, 58°C for fifteen seconds, and 74°C for one minute. The reaction mixture is electrophoresed on a 1% agarose gel, and a single band migrating at approximately 1600 base pairs is excised and purified through a Genelute® column. This fragment
25 is digested with Spe I and Not I, purified with a PCR Clean-up kit (Qiagen, Chatsworth, California), and ligated into a plasmid containing the Fc region of human IgG also digested with Spe I and Not I. The Not I site introduces three alanine residues in place of
30 "WVA" in positions 530, 531 and 532 of the normal amino acid sequence of the extracellular region of the murine polypeptide, which allows for an in frame ligation between the murine polypeptide sequence and the Fc sequence. Bacterial host cells are then transformed
35 with this plasmid and grown overnight. The plasmid DNA

is isolated from the bacteria host cells using the Qiagen miniprep protocol, and then digested with Spe I and Not I to confirm the presence and size of the inserts. One clone containing an insert of
5 approximately 1.6 kilobases is sequenced and shown to encode: amino acid residues 1-529 of the extracellular region of murine polypeptide in frame with the human IgG Fc region (SEQ ID NO: 61 and SEQ ID NO: 62 for DNA and amino acid sequences, respectively, with Fc portion
10 beginning at position 533 of the amino acid sequence).

Biology

As mentioned, Delta-Notch signaling is known to
15 regulate cell development, and more specifically, the differentiation of endothelial cells into more specialized cells. The studies shown in Examples 4 and 5, in particular, reveal that the polypeptide is strongly expressed in the vascular endothelium in both
20 the embryonic and adult stages, consequently it is not limited to organism development alone but has a role in adult organism biology as well. In the particular case of angiogenesis, Delta-Notch signaling would be expected to influence the development of endothelium
25 into blood vessels. Because the development of blood vessels are critical for the support of tumor growth, the linking of the polypeptide to angiogenesis could provide a "target" for use in programs for the identification and/or development of a suitable agonist
30 (stimulator) or antagonist (inhibitor) of its effect.

Specific examples of other endothelial cell biology that may be influenced include endothelial cell proliferation, migration, chemotaxis, changes vascular
35 permeability (possibly associated with inflammation), stimulation of endothelial cell production of other

factors (for example, metalloproteinases, growth factors, and angiogenesis inhibitors), and apoptosis.

The invention described above is now defined in
5 the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

- 5 1. A purified mammalian polypeptide comprising
an amino acid sequence selected from the group
consisting of:
- 10 (a) the polypeptide of SEQ ID NO: 2, SEQ ID NO:5,
SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ
ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ
ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ
ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 SEQ
ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ
ID NO: 21, or SEQ ID NO: 22;
- 15 (b) the polypeptide of SEQ ID NO: 4, SEQ ID NO:
23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO:
26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO:
29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO:
20 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO:
35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO:
38, SEQ ID NO: 39, or SEQ ID NO: 40;
- 25 (c) a polypeptide fragment of any of the
foregoing,
- 30 (d) a polypeptide analog of any of the foregoing
having at least eighty percent amino acid
sequence identity therewith,
- (e) any of the foregoing also having an
N-terminal methionyl residue.

2. The polypeptide according to claim 1 which is a human polypeptide comprising the amino acid sequence of SEQ ID NO: 26, with or without an N-terminal methionine residue.

5

3. A polypeptide analog according to claim 1 which is ninety percent or more identical in amino acid sequence with any of (a), (b), (c), (d) or (e).

10

4. A polypeptide according to claims 1, 2, or 3 which has been produced by recombinant expression.

5. A biologically active derivative of a polypeptide according to claim 1.

15

6. The polypeptide derivative of claim 5, in which the polypeptide is attached to a synthetic water soluble polymer, a detectable label molecule, or a polyamino acid.

20

7. The polypeptide derivative of claim 6 in which the synthetic water soluble polymer is polyethylene glycol or dextran.

25

8. The polypeptide derivative of claim 6 which is an Fc fusion product.

9. An isolated DNA molecule encoding a polypeptide according to claim 1 which is selected from the group consisting of:

30

(a) the DNA molecule of SEQ ID NO: 1 or SEQ ID NO: 3,

(b) an allelic variant of the DNA molecule of (a) which encodes the same polypeptide,

35

- (c) a DNA molecule which selectively hybridizes to the DNA molecule of (a) or (b), and
- (d) a DNA molecule which, but for the degeneracy of the genetic code, would hybridize to a DNA molecule of (a), (b) or (c).

10. A biologically functional viral or plasmid vector containing a DNA molecule according to claim 9.

11. A prokaryotic or eukaryotic host cell containing the vector of claim 10.

12. A host cell modified so that the expression of an endogenous polypeptide having the sequence of SEQ ID NO: 2 or SEQ ID NO: 4 or a fragment or naturally occurring mutation thereof is enhanced.

13. A host cell according to claim 12 which is an isolated human host cell.

14. A process for producing a polypeptide according to claim 1, which comprises culturing, under suitable nutrient conditions, a host cell containing a DNA molecule encoding the polypeptide such that expression of the polypeptide occurs, obtaining the polypeptide so produced, and optionally preparing a composition containing the polypeptide.

15. An antibody for the polypeptide of claim 1.

16. The antibody of claim 15 which is monoclonal.

17. A method for identifying a receptor which binds to the polypeptide of claim 1, comprising the

polypeptide with a receptor to be identified under conditions to permit binding, and detecting the presence of any binding.

- 5 18. A transgenic non-human mammal capable of expressing in any cell thereof the DNA of SEQ ID NO: 3.

1 / 2 4

FIG. 1A

ATGACGCCTG CGTCCCGGAG CGCCTGTCGC TGGGCGCTAC TGCTGCTGGC
GGTACTGTGG CCGCAGCAGC GCGCTGCGGG CTCCGGCATC TTCCAGCTGC
GGCTGCAGGA GTTCGTCAAC CAGCGCGGTA TGCTGGCCAA TGGGCAGTCC
TGCGAACCGG GCTGCCGGAC TTTCTTCCGC ATTTGCCTTA AGCACTTCCA
GGCAACCTTC TCCGAGGGAC CCTGCACCTT TGGCAATGTC TCCACGCCGG
TATTGGGCAC CAACTCCTTC GTCGTCAGGG ACAAGAATAG CGGCAGTGGT
CGCAACCCTC TGCAGTTGCC CTTCAATTTT ACCTGGCCGG GAACCTTCTC
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GGTCCAGTTA TGCCTGCGAA TGCCCCCCCCA ACTTTACCGG CTCTAACTGT
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FIG. 1B

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CAGGCACCCA CTGTGAACTG CACATCAGCG ATTGTGCCCCG AAGTCCCTGT
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FIG. 2

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KPECRISAIC SPRDSMYQSV CLISEERNEC VIATEV

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FIG. 3A

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FIG. 3B

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FIG. 4

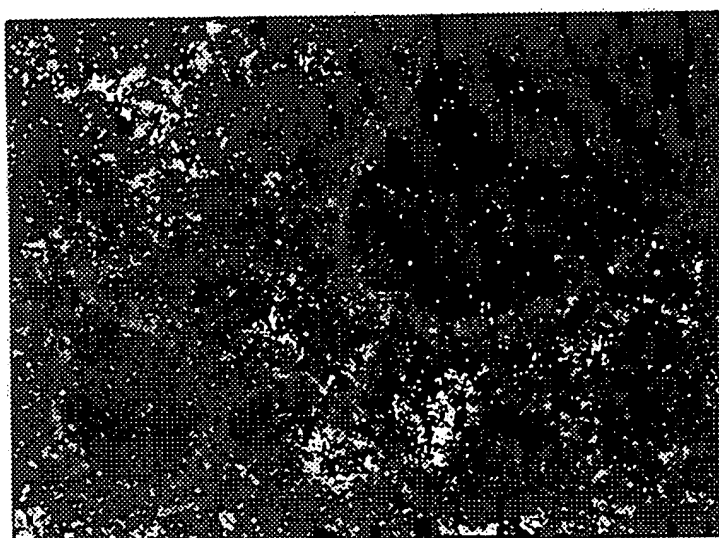
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FIG. 5A



FIG. 5B



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FIG. 5C

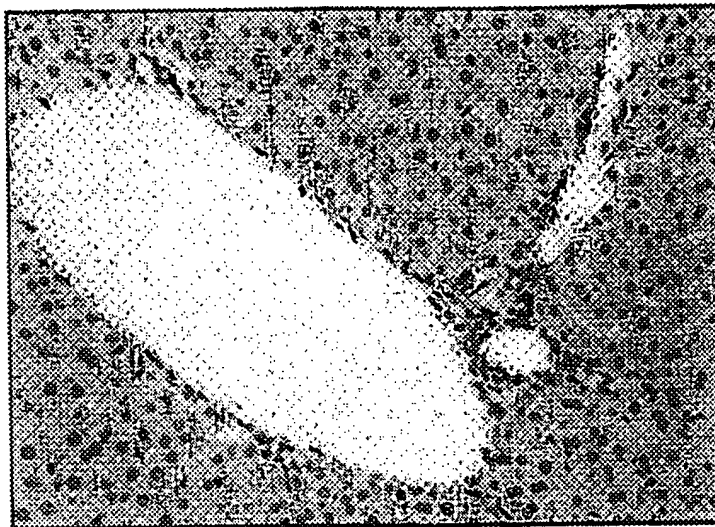
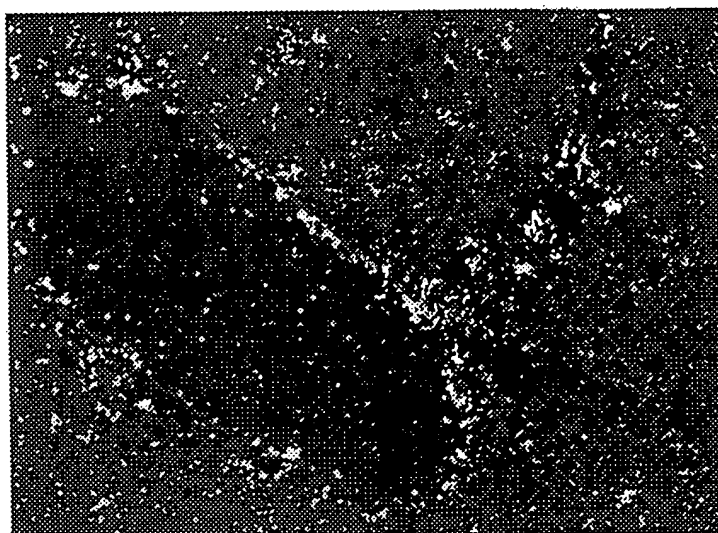


FIG. 5D



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FIG. 5E

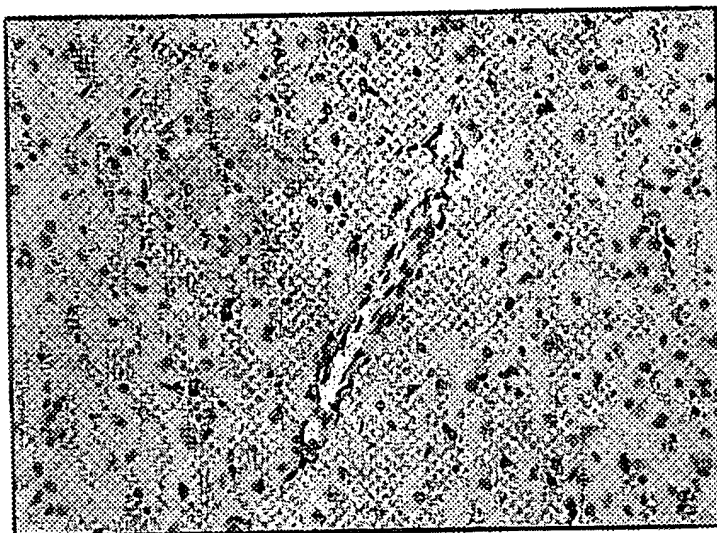
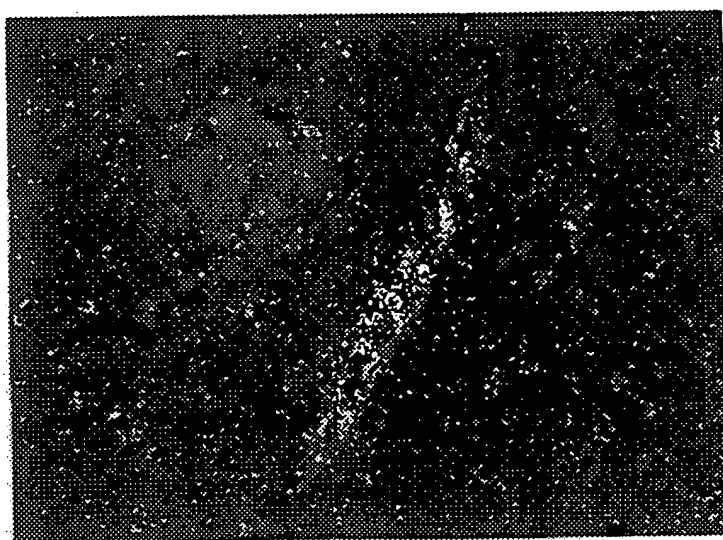


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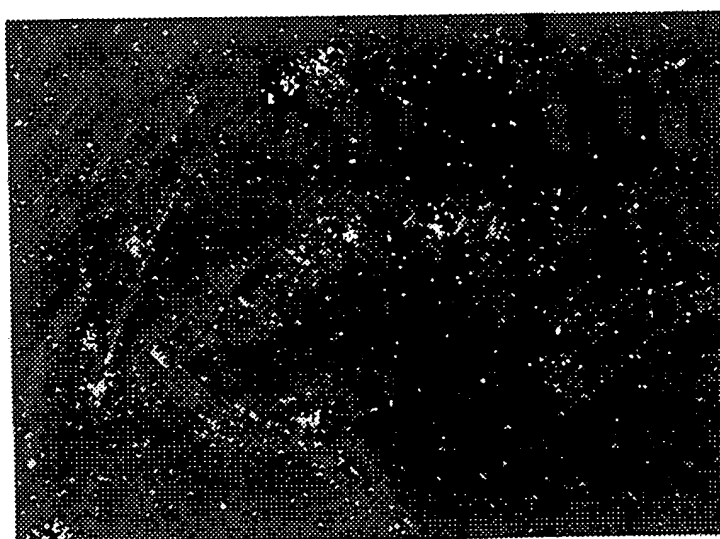


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FIG. 5G



FIG. 5H

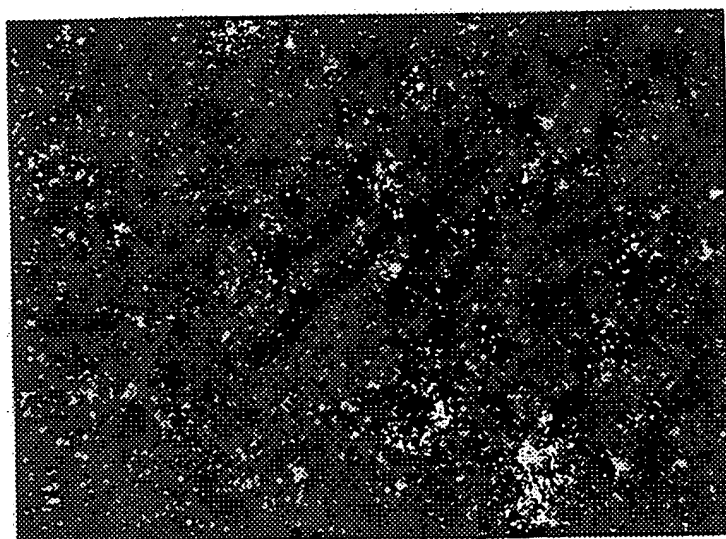


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FIG. 5I



FIG. 5J

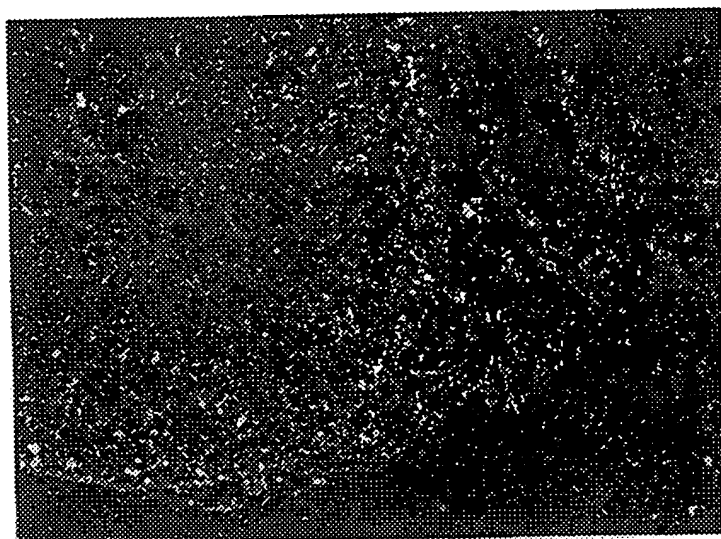


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FIG. 5K



FIG. 5L

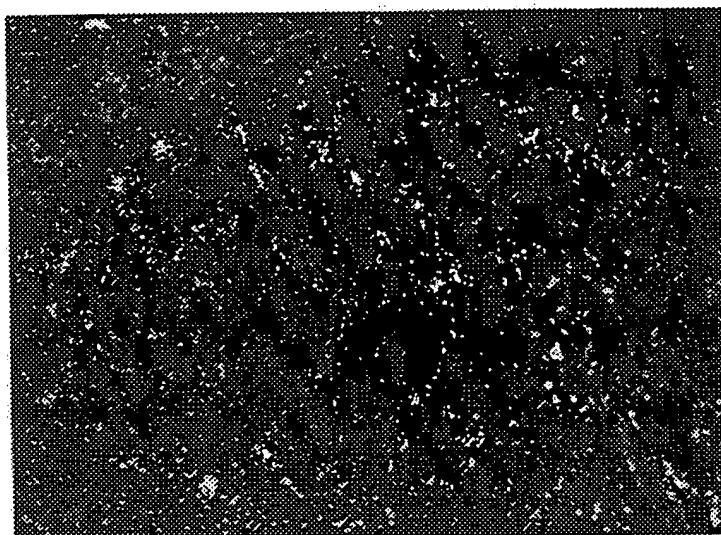


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FIG. 5M



FIG. 5N



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FIG. 50

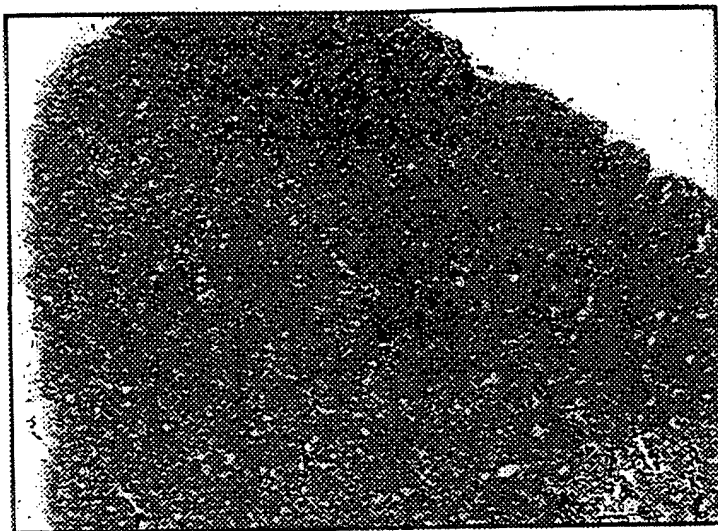
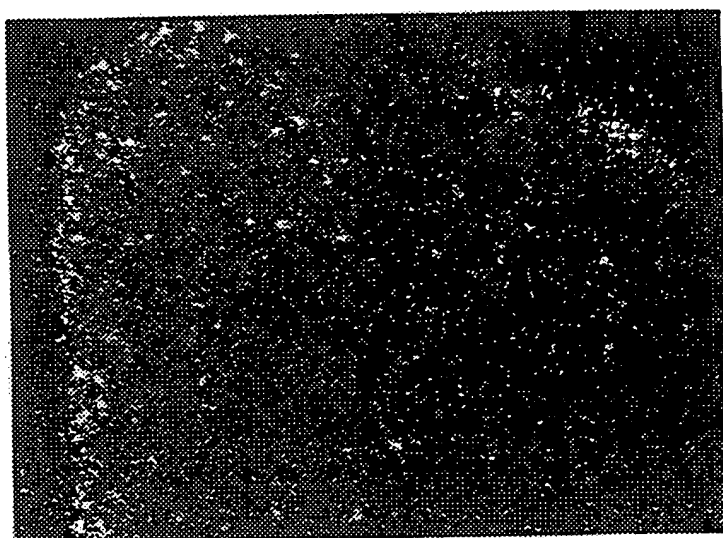


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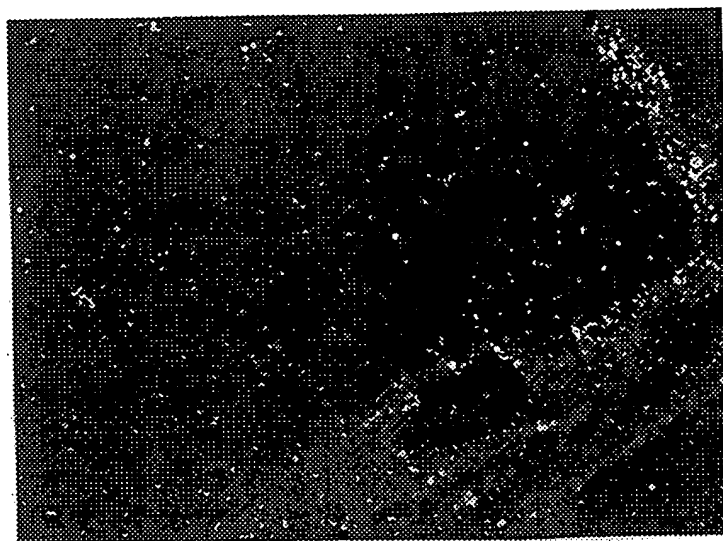


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FIG. 6A



FIG. 6B



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FIG. 6C

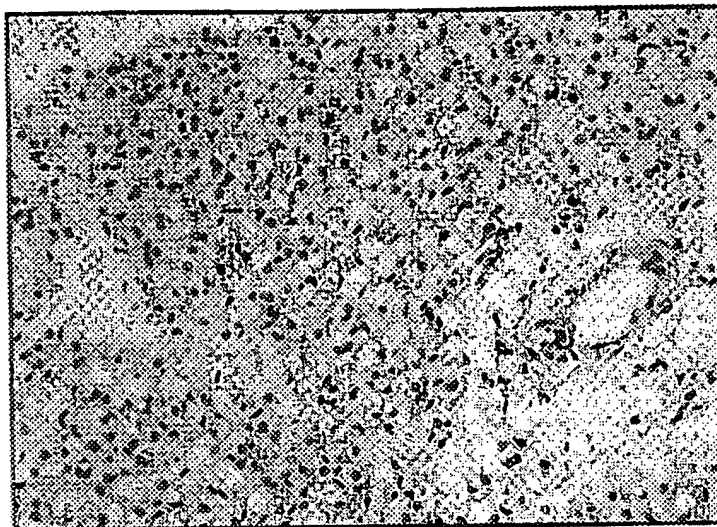
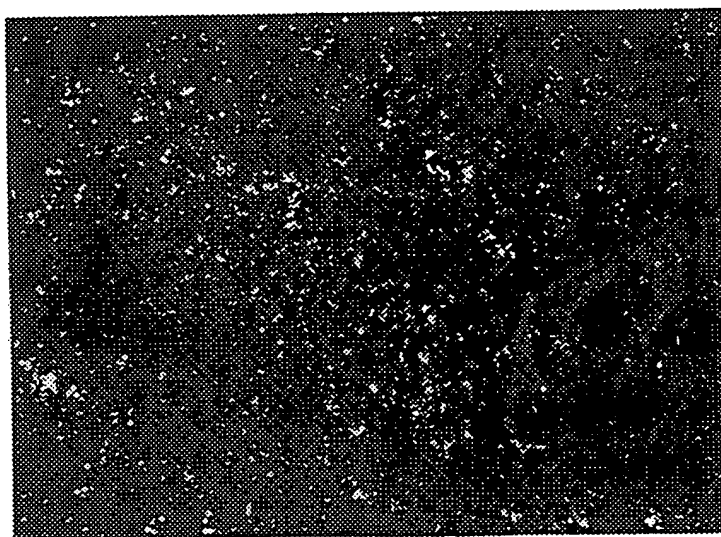


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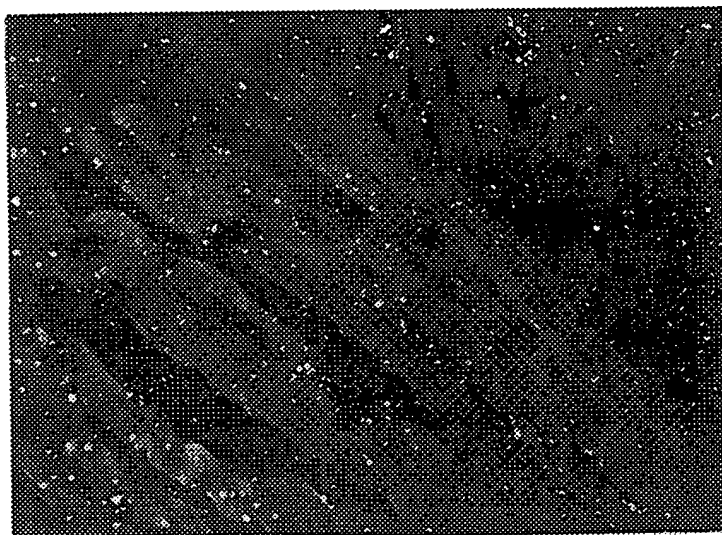


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FIG. 6E



FIG. 6F

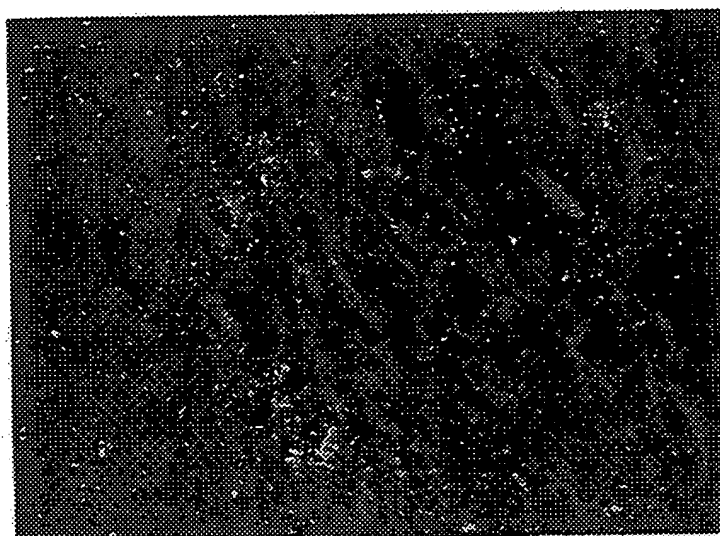


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FIG. 6G



FIG. 6H



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FIG. 6I

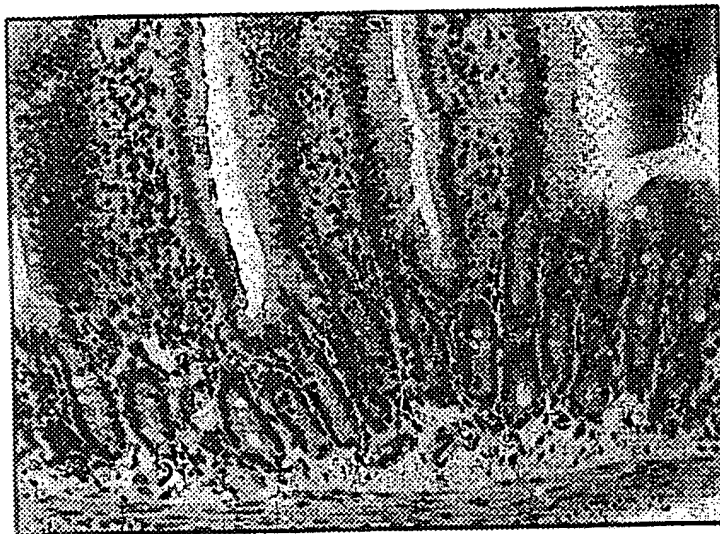
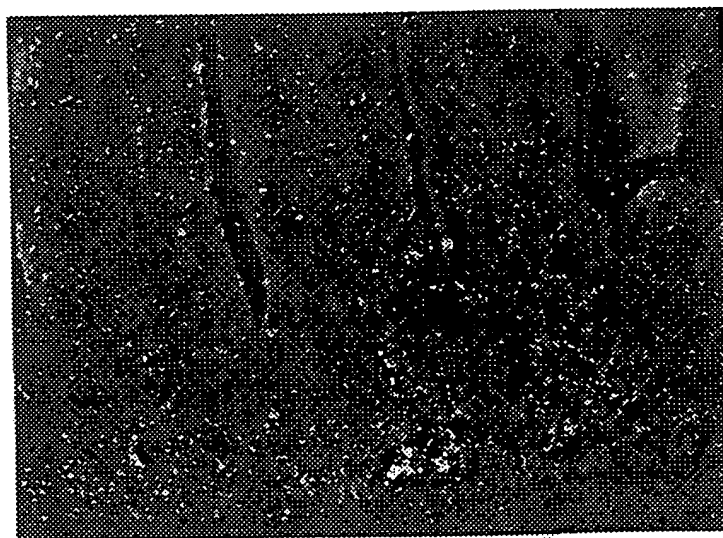


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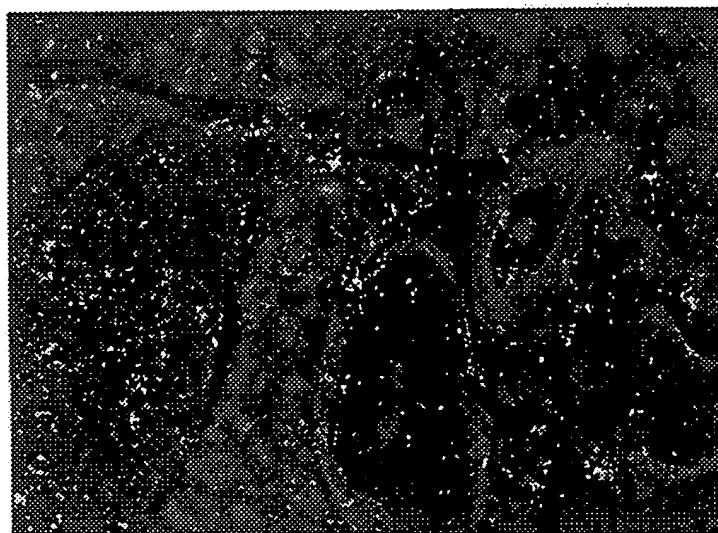


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FIG. 6K



FIG. 6L



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FIG. 6M

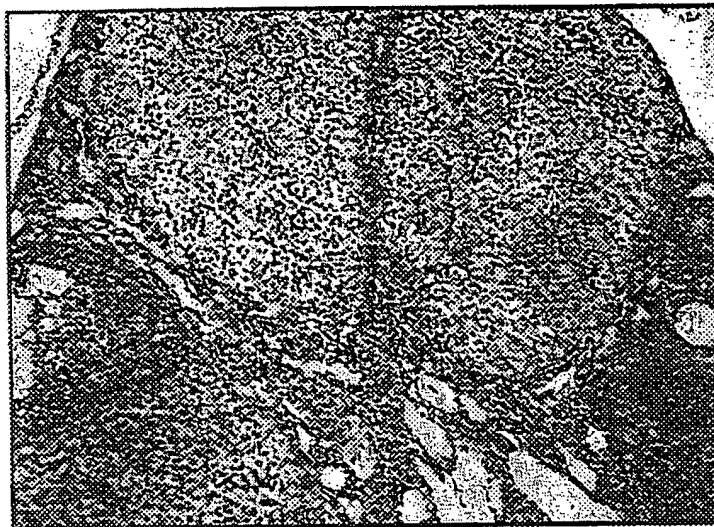
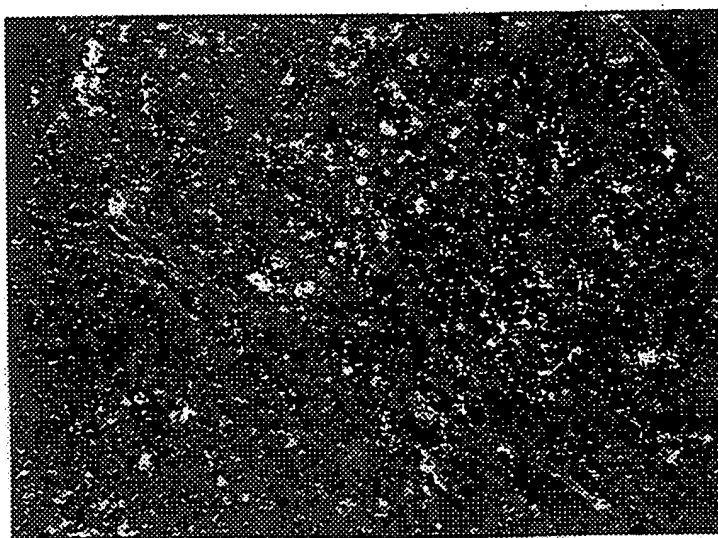


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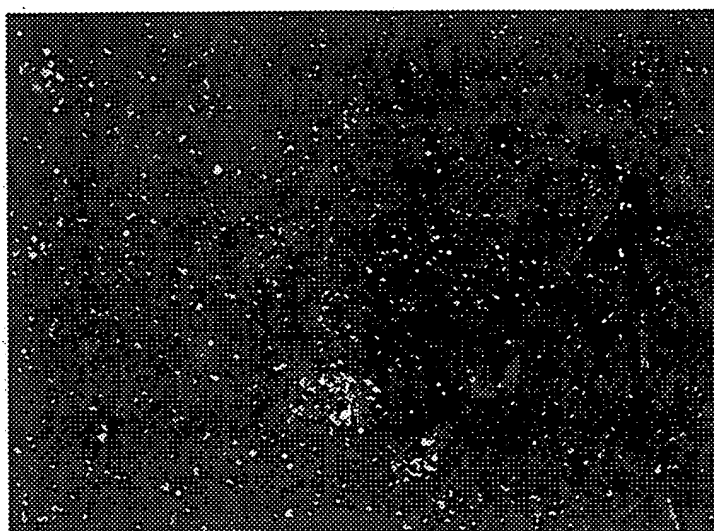


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FIG. 6O



FIG. 6P



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FIG. 7A

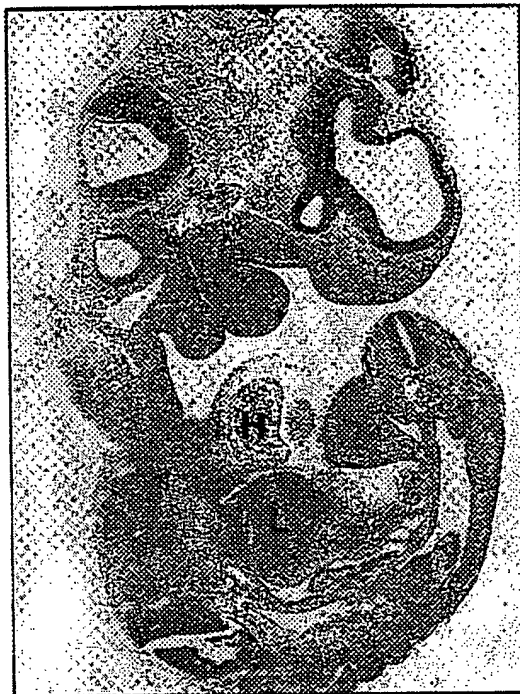
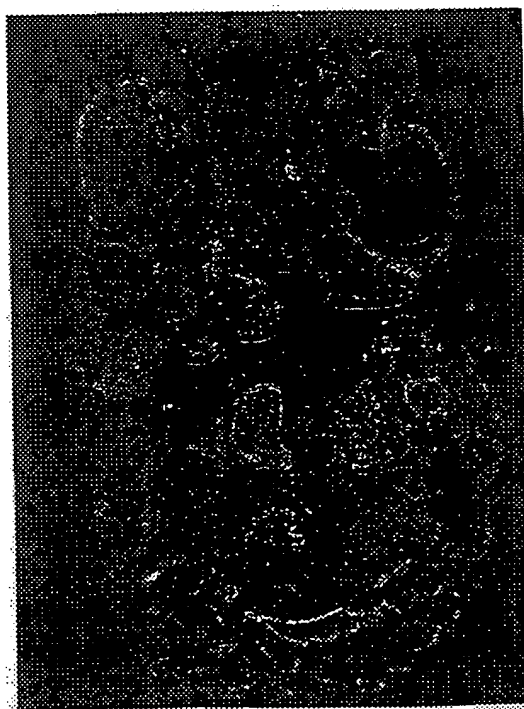


FIG. 7B



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FIG. 7C

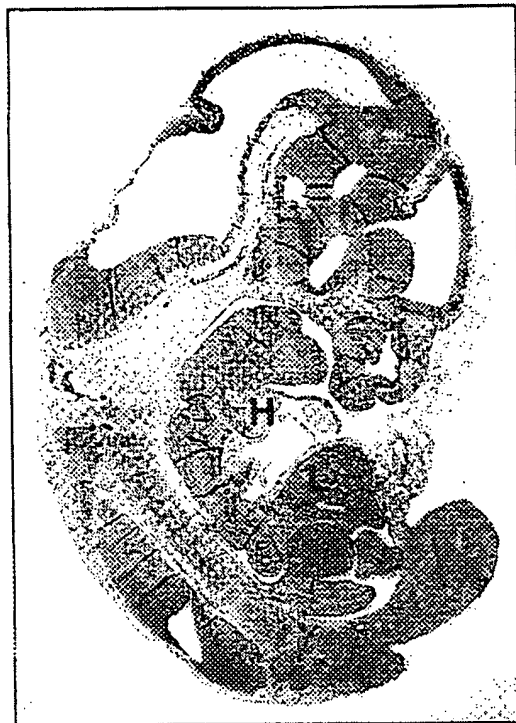
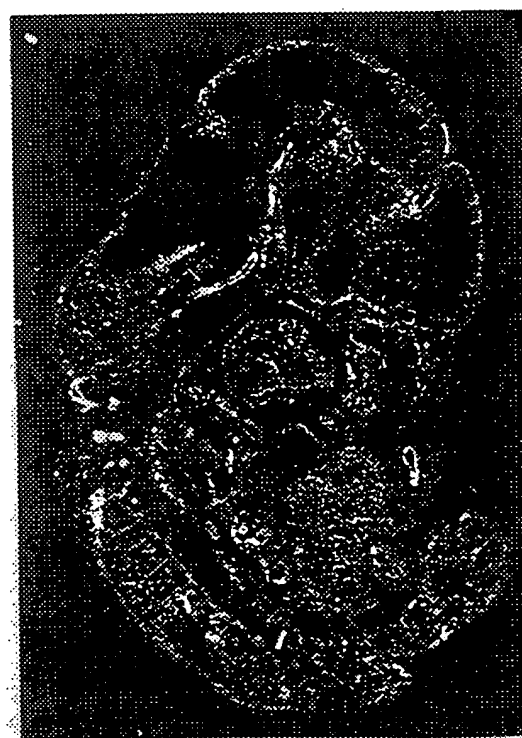


FIG. 7D



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gcttggcacg cgccaggaga cgacctgcgg ccagaggcct tgccaccaga tgcactcatc 420
agcaagatcg ccatccaggg ctccctagct gtgggtcaga actgggttatt ggatgagcaa 480
accagcacc cacaagggt ggcgtactct taccgggtca tctgcagtga caactactat 540
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cagccagatg gcaacttgct ctgctgccc ggttgactg gggaatattg ccaacagcct 660
atctgtcttt cgggctgtca tgaacagaat ggctactgca gcaagccagc agagtgcctc 720
tgccgcccag gctggcaggg cgggctgtgt aacgaatgca tccccacaa tggctgtcgc 780
cacggcacct gcagcactcc ctggcaatgt acttgtagt agggctgggg aggcctgttt 840
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tccaacagtg ggcagcgaag ctacacctgc acctgtcgcc caggctacac tgggtgtggac 960
tgtgagctgg agctcagcga gtgtgacagc aacctctgtc gcaatggagg cagctgtaag 1020
gaccaggagg atggctacca ctgctgtgt cctccgggct actatggcct gcattgtgaa 1080
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gacaagtcca actgtggcaa acagcaaac cagcatttgg actataatct ggccccaggg 1860
cccctggggc gggggacat gccaggaaag tttcccaca gtgacaagag cttaggagag 1920
aaggcgccac tgcggttaca cagtgaagag ccagagtgtc ggatatcagc gatatgctcc 1980
cccagggact ccatgtacca gtctgtgtgt ttgatatcag aggagaggaa tgaatgtgtc 2040
attgccacgg aggta 2055
  
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<210> 4
 <211> 685
 <212> PRT
 <213> Human

<400> 4

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Met Ala Ala Ala Ser Arg Ser Ala Ser Gly Trp Ala Leu Leu Leu Leu
  1           5           10           15

Val Ala Leu Trp Gln Gln Arg Ala Ala Gly Ser Gly Val Phe Gln Leu
          20           25           30

Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu Ala Ser Gly Arg
      35           40           45
  
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Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val Cys Leu Lys His
 50 55 60
 Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe Gly Thr Val Ser
 65 70 75 80
 Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg Asp Asp Ser Ser
 85 90 95
 Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro
 100 105 110
 Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala Pro Gly Asp Asp
 115 120 125
 Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile Ser Lys Ile Ala
 130 135 140
 Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu Leu Asp Glu Gln
 145 150 155 160
 Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg Val Ile Cys Ser
 165 170 175
 Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys Lys Lys Arg Asn
 180 185 190
 Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly Asn Leu Ser Cys
 195 200 205
 Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro Ile Cys Leu Ser
 210 215 220
 Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Ala Glu Cys Leu
 225 230 235 240
 Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His
 245 250 255
 Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp Gln Cys Thr Cys
 260 265 270
 Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys
 275 280 285
 Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys Ser Asn Ser Gly
 290 295 300
 Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr Thr Gly Val Asp
 305 310 315 320
 Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro Cys Arg Asn Gly
 325 330 335
 Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys Leu Cys Pro Pro
 340 345 350
 Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu Ser Cys Ala Asp
 355 360 365
 Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ala
 370 375 380

Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu
 385 390 395 400
 Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln
 405 410 415
 Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys Arg Pro Gly Phe
 420 425 430
 Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys Ala Arg Asn Pro
 435 440 445
 Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Leu Met Cys
 450 455 460
 Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu Val Arg Thr Ser
 465 470 475 480
 Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg Ala Thr Cys Tyr
 485 490 495
 Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys Pro Tyr Gly Phe
 500 505 510
 Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro
 515 520 525
 Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala Val Leu Leu Val Leu
 530 535 540
 Leu Gly Met Val Ala Val Ala Val Arg Gln Leu Arg Leu Arg Arg Pro
 545 550 555 560
 Asp Asp Gly Ser Arg Glu Ala Met Asn Asn Leu Ser Asp Phe Gln Lys
 565 570 575
 Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys
 580 585 590
 Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys Gln
 595 600 605
 Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly Pro Leu Gly Arg
 610 615 620
 Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp Lys Ser Leu Gly Glu
 625 630 635 640
 Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro Glu Cys Arg Ile Ser
 645 650 655
 Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile
 660 665 670
 Ser Glu Glu Arg Asn Glu Cys Val Ile Ala Thr Glu Val
 675 680 685

<210> 5
 <211> 510
 <212> PRT
 <213> Murine

<400> 5

Gln Arg Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe
 1 5 10 15
 Val Asn Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly
 20 25 30
 Cys Arg Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe
 35 40 45
 Ser Glu Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly
 50 55 60
 Thr Asn Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn
 65 70 75 80
 Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu
 85 90 95
 Asn Ile Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr
 100 105 110
 Ser Pro Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu
 115 120 125
 Ala Val Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr
 130 135 140
 Arg Leu Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly
 145 150 155 160
 Glu Ser Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His
 165 170 175
 Tyr Glu Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr
 180 185 190
 Gly Lys Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln
 195 200 205
 Asn Gly Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp
 210 215 220
 Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His
 225 230 235 240
 Gly Thr Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly
 245 250 255
 Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro
 260 265 270
 Cys Lys Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr
 275 280 285
 Cys Thr Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu
 290 295 300
 Ser Lys Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp
 305 310 315 320
 Gln Glu Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln
 325 330 335

His Cys Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn
 340 345 350
 Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu
 355 360 365
 Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg
 370 375 380
 Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly
 385 390 395 400
 Pro Ser Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys
 405 410 415
 Glu Leu His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly
 420 425 430
 Thr Cys His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly
 435 440 445
 Phe Ser Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala
 450 455 460
 Ser Gly Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro
 465 470 475 480
 Asn Asn Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys
 485 490 495
 Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505 510

<210> 6
 <211> 509
 <212> PRT
 <213> Murine

<400> 6

Arg Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val
 1 5 10 15
 Asn Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys
 20 25 30
 Arg Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser
 35 40 45
 Glu Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr
 50 55 60
 Asn Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro
 65 70 75 80
 Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn
 85 90 95
 Ile Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser
 100 105 110

Pro Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala
 115 120 125
 Val Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg
 130 135 140
 Leu Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu
 145 150 155 160
 Ser Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr
 165 170 175
 Glu Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly
 180 185 190
 Lys Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn
 195 200 205
 Gly Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln
 210 215 220
 Gly Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly
 225 230 235 240
 Thr Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly
 245 250 255
 Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys
 260 265 270
 Lys Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys
 275 280 285
 Thr Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser
 290 295 300
 Lys Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln
 305 310 315 320
 Glu Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His
 325 330 335
 Cys Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly
 340 345 350
 Gly Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys
 355 360 365
 Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys
 370 375 380
 Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro
 385 390 395 400
 Ser Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu
 405 410 415
 Leu His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr
 420 425 430
 Cys His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe
 435 440 445

Ser Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser
 450 455 460
 Gly Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn
 465 470 475
 Asn Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu
 485 490 495
 Phe Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 7
 <211> 508
 <212> PRT
 <213> Murine

<400> 7

Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn
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 Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg
 20 25 30
 Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu
 35 40 45
 Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn
 50 55 60
 Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu
 65 70 75 80
 Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile
 85 90 95
 Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro
 100 105 110
 Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val
 115 120 125
 Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu
 130 135 140
 Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser
 145 150 155 160
 Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu
 165 170 175
 Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys
 180 185 190
 Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly
 195 200 205
 Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly
 210 215 220
 Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr
 225 230 235 240

Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu
 245 250 255
 Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys
 260 265 270
 Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr
 275 280 285
 Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys
 290 295 300
 Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu
 305 310 315 320
 Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys
 325 330 335
 Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly
 340 345 350
 Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro
 355 360 365
 Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr
 370 375 380
 Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser
 385 390 395 400
 Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu
 405 410 415
 His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys
 420 425 430
 His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser
 435 440 445
 Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly
 450 455 460
 Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn
 465 470 475 480
 Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe
 485 490 495
 Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 8
 <211> 507
 <212> PRT
 <213> Murine

<400> 8

Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln
 1 5 10 15

Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr
 20 25 30
 Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly
 35 40 45
 Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser
 50 55 60
 Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln
 65 70 75 80
 Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln
 85 90 95
 Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly
 100 105 110
 Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly
 115 120 125
 Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser
 130 135 140
 Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys
 145 150 155 160
 Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys
 165 170 175
 Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr
 180 185 190
 Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr
 195 200 205
 Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg
 210 215 220
 Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys
 225 230 235 240
 Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe
 245 250 255
 Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn
 260 265 270
 Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys
 275 280 285
 Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys
 290 295 300
 Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn
 305 310 315 320
 Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu
 325 330 335
 His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser
 340 345 350

Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro
 355 360 365
 Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser
 370 375 380
 Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg
 385 390 395 400
 Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His
 405 410 415
 Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His
 420 425 430
 Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly
 435 440 445
 Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro
 450 455 460
 Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe
 465 470 475 480
 Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro
 485 490 495
 Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 9
 <211> 506
 <212> PRT
 <213> Murine

<400> 9

Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln Arg
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 Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe
 20 25 30
 Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly Pro
 35 40 45
 Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe
 50 55 60
 Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu
 65 70 75 80
 Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala
 85 90 95
 Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn
 100 105 110
 Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly Lys
 115 120 125
 Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr
 130 135 140

Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser
 145 150 155 160
 Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln
 165 170 175
 Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys
 180 185 190
 Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys
 195 200 205
 Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu
 210 215 220
 Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser
 225 230 235 240
 Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys
 245 250 255
 Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly
 260 265 270
 Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu
 275 280 285
 Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys Ala
 290 295 300
 Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser
 305 310 315 320
 Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu His
 325 330 335
 Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys
 340 345 350
 Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn
 355 360 365
 Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn
 370 375 380
 Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr
 385 390 395 400
 Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His Ile
 405 410 415
 Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His Asp
 420 425 430
 Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg
 435 440 445
 Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro Cys
 450 455 460
 Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val
 465 470 475 480

Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val
485 490 495

Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
500 505

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<210> 10
<211> 505
<212> PRT
<213> Murine
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<400> 10

Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln Arg Gly
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Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe Phe
20 25 30

Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly Pro Cys
35 40 45

Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Val
50 55 60

Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu Pro
65 70 75 80

Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala Trp
85 90 95

His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn Ser
100 105 110

Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly Lys Ile
115 120 125

Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr Ser
130 135 140

Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser Arg
145 150 155 160

Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln Pro
165 170 175

Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys Asp
180 185 190

Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser
195 200 205

Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys
210 215 220

Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Ile
225 230 235 240

Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp
245 250 255

Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ser
260 265 270

Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu Pro
 275 280 285
 Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys Ala Ser
 290 295 300
 Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser Tyr
 305 310 315 320
 His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu His Ser
 325 330 335
 Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg
 340 345 350
 Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn Phe
 355 360 365
 Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro
 370 375 380
 Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr Cys
 385 390 395 400
 Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His Ile Ser
 405 410 415
 Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His Asp Leu
 420 425 430
 Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg
 435 440 445
 Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro Cys Phe
 450 455 460
 Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val Cys
 465 470 475 480
 Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly
 485 490 495
 Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 11
 <211> 531
 <212> PRT
 <213> Murine

<220>
 <223> Murine protein sequence (less signal sequence and
 intracellular domain)

<400> 11

Gln Arg Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe
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 Val Asn Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly
 20 25 30

Cys Arg Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe
 35 40 45
 Ser Glu Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly
 50 55 60
 Thr Asn Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn
 65 70 75 80
 Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu
 85 90 95
 Asn Ile Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr
 100 105 110
 Ser Pro Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu
 115 120 125
 Ala Val Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr
 130 135 140
 Arg Leu Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly
 145 150 155 160
 Glu Ser Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His
 165 170 175
 Tyr Glu Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr
 180 185 190
 Gly Lys Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln
 195 200 205
 Asn Gly Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp
 210 215 220
 Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His
 225 230 235 240
 Gly Thr Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly
 245 250 255
 Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro
 260 265 270
 Cys Lys Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr
 275 280 285
 Cys Thr Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu
 290 295 300
 Ser Lys Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp
 305 310 315 320
 Gln Glu Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln
 325 330 335
 His Cys Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn
 340 345 350
 Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu
 355 360 365

Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg
 370 375 380
 Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly
 385 390 395 400
 Pro Ser Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys
 405 410 415
 Glu Leu His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly
 420 425 430
 Thr Cys His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly
 435 440 445
 Phe Ser Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala
 450 455 460
 Ser Gly Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro
 465 470 475 480
 Asn Asn Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys
 485 490 495
 Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser
 500 505 510
 Leu Gly Val Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val
 515 520 525
 Val Ala Val
 530

<210> 12

<211> 530

<212> PRT

<213> Murine

<220>

<223> Murine protein sequence (less signal sequence and
 intracellular domain)

<400> 12

Arg Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val
 1 5 10 15
 Asn Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys
 20 25 30
 Arg Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser
 35 40 45
 Glu Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr
 50 55 60
 Asn Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro
 65 70 75 80
 Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn
 85 90 95

Ile Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser
 100 105 110
 Pro Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala
 115 120 125
 Val Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg
 130 135 140
 Leu Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu
 145 150 155 160
 Ser Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr
 165 170 175
 Glu Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly
 180 185 190
 Lys Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn
 195 200 205
 Gly Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln
 210 215 220
 Gly Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly
 225 230 235 240
 Thr Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly
 245 250 255
 Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys
 260 265 270
 Lys Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys
 275 280 285
 Thr Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser
 290 295 300
 Lys Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln
 305 310 315 320
 Glu Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His
 325 330 335
 Cys Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly
 340 345 350
 Gly Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys
 355 360 365
 Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys
 370 375 380
 Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro
 385 390 395 400
 Ser Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu
 405 410 415
 Leu His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr
 420 425 430

[illegible]

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<210> 13
<211> 529
<212> PRT
<213> Murine
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<220>
<223> Murine protein sequence (less signal sequence and
intracellular domain)
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<400> 13

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ala | Gly | Ser | Gly | Ile | Phe | Gln | Leu | Arg | Leu | Gln | Glu | Phe | Val | Asn |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Gln | Arg | Gly | Met | Leu | Ala | Asn | Gly | Gln | Ser | Cys | Glu | Pro | Gly | Cys | Arg |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Thr | Phe | Phe | Arg | Ile | Cys | Leu | Lys | His | Phe | Gln | Ala | Thr | Phe | Ser | Glu |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Gly | Pro | Cys | Thr | Phe | Gly | Asn | Val | Ser | Thr | Pro | Val | Leu | Gly | Thr | Asn |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Ser | Phe | Val | Val | Arg | Asp | Lys | Asn | Ser | Gly | Ser | Gly | Arg | Asn | Pro | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Gln | Leu | Pro | Phe | Asn | Phe | Thr | Trp | Pro | Gly | Thr | Phe | Ser | Leu | Asn | Ile |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Gln | Ala | Trp | His | Thr | Pro | Gly | Asp | Asp | Leu | Arg | Pro | Glu | Thr | Ser | Pro |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Gly | Asn | Ser | Leu | Ile | Ser | Gln | Ile | Ile | Ile | Gln | Gly | Ser | Leu | Ala | Val |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Gly | Lys | Ile | Trp | Arg | Thr | Asp | Glu | Gln | Asn | Asp | Thr | Leu | Thr | Arg | Leu |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Ser | Tyr | Ser | Tyr | Arg | Val | Ile | Cys | Ser | Asp | Asn | Tyr | Tyr | Gly | Glu | Ser |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu
 165 170 175
 Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys
 180 185 190
 Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly
 195 200 205
 Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly
 210 215 220
 Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr
 225 230 235 240
 Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu
 245 250 255
 Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys
 260 265 270
 Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr
 275 280 285
 Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys
 290 295 300
 Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu
 305 310 315 320
 Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys
 325 330 335
 Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly
 340 345 350
 Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro
 355 360 365
 Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr
 370 375 380
 Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser
 385 390 395 400
 Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu
 405 410 415
 His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys
 420 425 430
 His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser
 435 440 445
 Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly
 450 455 460
 Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn
 465 470 475 480
 Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe
 485 490 495

Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly
 500 505 510
 Val Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala
 515 520 525
 Val

<210> 14
 <211> 528
 <212> PRT
 <213> Murine

<220>
 <223> Murine protein sequence (less signal sequence and
 intracellular domain)

<400> 14

Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln
 1 5 10 15
 Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr
 20 25 30
 Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly
 35 40 45
 Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser
 50 55 60
 Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln
 65 70 75 80
 Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln
 85 90 95
 Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly
 100 105 110
 Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly
 115 120 125
 Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser
 130 135 140
 Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys
 145 150 155 160
 Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys
 165 170 175
 Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr
 180 185 190
 Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr
 195 200 205
 Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg
 210 215 220

Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys
 225 230 235 240
 Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe
 245 250 255
 Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn
 260 265 270
 Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys
 275 280 285
 Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys
 290 295 300
 Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn
 305 310 315 320
 Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu
 325 330 335
 His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser
 340 345 350
 Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro
 355 360 365
 Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser
 370 375 380
 Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg
 385 390 395 400
 Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His
 405 410 415
 Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His
 420 425 430
 Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly
 435 440 445
 Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro
 450 455 460
 Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe
 465 470 475 480
 Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro
 485 490 495
 Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val
 500 505 510
 Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala Val
 515 520 525

<210> 15
 <211> 527
 <212> PRT
 <213> Murine

<220>
 <223> Murine protein sequence (less signal sequence and
 intracellular domain)

<400> 15

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Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln Arg
 1           5           10           15
Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe
          20           25           30
Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly Pro
          35           40           45
Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe
          50           55           60
Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu
          65           70           75           80
Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala
          85           90           95
Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn
          100          105          110
Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly Lys
          115          120          125
Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr
          130          135          140
Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser
          145          150          155          160
Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln
          165          170          175
Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys
          180          185          190
Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys
          195          200          205
Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu
          210          215          220
Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser
          225          230          235          240
Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys
          245          250          255
Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly
          260          265          270
Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu
          275          280          285

```


Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys Ala
 290 295 300
 Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser
 305 310 315 320
 Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu His
 325 330 335
 Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys
 340 345 350
 Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn
 355 360 365
 Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn
 370 375 380
 Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr
 385 390 395 400
 Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His Ile
 405 410 415
 Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His Asp
 420 425 430
 Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg
 435 440 445
 Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro Cys
 450 455 460
 Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val
 465 470 475 480
 Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val
 485 490 495
 Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly
 500 505 510
 Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala Val
 515 520 525

<210> 16

<211> 526

<212> PRT

<213> Murine

<220>

<223> Murine protein sequence (less signal sequence and
 intracellular domain)

<400> 16

Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln Arg Gly
 1 5 10 15
 Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe Phe
 20 25 30

Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly Pro Cys
 35 40 45
 Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Val
 50 55 60
 Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu Pro
 65 70 75 80
 Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala Trp
 85 90 95
 His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn Ser
 100 105 110
 Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly Lys Ile
 115 120 125
 Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr Ser
 130 135 140
 Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser Arg
 145 150 155 160
 Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln Pro
 165 170 175
 Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys Asp
 180 185 190
 Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser
 195 200 205
 Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys
 210 215 220
 Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Ile
 225 230 235 240
 Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp
 245 250 255
 Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ser
 260 265 270
 Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu Pro
 275 280 285
 Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys Ala Ser
 290 295 300
 Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser Tyr
 305 310 315 320
 His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu His Ser
 325 330 335
 Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg
 340 345 350
 Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn Phe
 355 360 365

Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro
 370 375 380
 Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr Cys
 385 390 395 400
 Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His Ile Ser
 405 410 415
 Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His Asp Leu
 420 425 430
 Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg
 435 440 445
 Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro Cys Phe
 450 455 460
 Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val Cys
 465 470 475 480
 Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly
 485 490 495
 Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu
 500 505 510
 Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala Val
 515 520 525

<210> 17

<211> 664

<212> PRT

<213> Murine

<220>

<223> Murine protein sequence (less signal sequence)

<400> 17

Gln Arg Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe
 1 5 10 15
 Val Asn Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly
 20 25 30
 Cys Arg Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe
 35 40 45
 Ser Glu Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly
 50 55 60
 Thr Asn Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn
 65 70 75 80
 Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu
 85 90 95
 Asn Ile Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr
 100 105 110
 Ser Pro Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu
 115 120 125

Ala Val Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr
 130 135 140
 Arg Leu Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly
 145 150 155 160
 Glu Ser Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His
 165 170 175
 Tyr Glu Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr
 180 185 190
 Gly Lys Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln
 195 200 205
 Asn Gly Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp
 210 215 220
 Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His
 225 230 235 240
 Gly Thr Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly
 245 250 255
 Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro
 260 265 270
 Cys Lys Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr
 275 280 285
 Cys Thr Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu
 290 295 300
 Ser Lys Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp
 305 310 315 320
 Gln Glu Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln
 325 330 335
 His Cys Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn
 340 345 350
 Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu
 355 360 365
 Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg
 370 375 380
 Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly
 385 390 395 400
 Pro Ser Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys
 405 410 415
 Glu Leu His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly
 420 425 430
 Thr Cys His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly
 435 440 445
 Phe Ser Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala
 450 455 460

Ser Gly Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro
 465 470 475 480
 Asn Asn Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys
 485 490 495
 Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser
 500 505 510
 Leu Gly Val Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val
 515 520 525
 Val Ala Val Arg Gln Leu Arg Leu Arg Arg Pro Asp Asp Glu Ser Arg
 530 535 540
 Glu Ala Met Asn Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro
 545 550 555 560
 Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp
 565 570 575
 Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys Leu Gln Asn His Thr Leu
 580 585 590
 Asp Tyr Asn Leu Ala Pro Gly Leu Leu Gly Arg Gly Ser Met Pro Gly
 595 600 605
 Lys Tyr Pro His Ser Asp Lys Ser Leu Gly Glu Lys Val Pro Leu Arg
 610 615 620
 Leu His Ser Glu Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro
 625 630 635 640
 Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn
 645 650 655
 Glu Cys Val Ile Ala Thr Glu Val
 660

<210> 18

<211> 663

<212> PRT

<213> Murine

<220>

<223> Murine protein sequence (less signal sequence)

<400> 18

Arg Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val
 1 5 10 15
 Asn Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys
 20 25 30
 Arg Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser
 35 40 45
 Glu Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr
 50 55 60
 Asn Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro
 65 70 75 80

| | | | | | | | | | | | | | | | |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Leu | Gln | Leu | Pro | Phe 85 | Asn | Phe | Thr | Trp | Pro 90 | Gly | Thr | Phe | Ser | Leu 95 | Asn |
| Ile | Gln | Ala | Trp 100 | His | Thr | Pro | Gly | Asp 105 | Asp | Leu | Arg | Pro | Glu 110 | Thr | Ser |
| Pro | Gly | Asn 115 | Ser | Leu | Ile | Ser | Gln 120 | Ile | Ile | Ile | Gln | Gly 125 | Ser | Leu | Ala |
| Val | Gly 130 | Lys | Ile | Trp | Arg | Thr 135 | Asp | Glu | Gln | Asn | Asp 140 | Thr | Leu | Thr | Arg |
| Leu 145 | Ser | Tyr | Ser | Tyr | Arg 150 | Val | Ile | Cys | Ser | Asp 155 | Asn | Tyr | Tyr | Gly | Glu 160 |
| Ser | Cys | Ser | Arg | Leu 165 | Cys | Lys | Lys | Arg | Asp 170 | Asp | His | Phe | Gly | His 175 | Tyr |
| Glu | Cys | Gln | Pro 180 | Asp | Gly | Ser | Leu | Ser 185 | Cys | Leu | Pro | Gly | Trp 190 | Thr | Gly |
| Lys | Tyr | Cys 195 | Asp | Gln | Pro | Ile | Cys 200 | Leu | Ser | Gly | Cys | His 205 | Glu | Gln | Asn |
| Gly | Tyr 210 | Cys | Ser | Lys | Pro | Asp 215 | Glu | Cys | Ile | Cys | Arg 220 | Pro | Gly | Trp | Gln |
| Gly 225 | Arg | Leu | Cys | Asn | Glu 230 | Cys | Ile | Pro | His | Asn 235 | Gly | Cys | Arg | His | Gly 240 |
| Thr | Cys | Ser | Ile | Pro 245 | Trp | Gln | Cys | Ala | Cys 250 | Asp | Glu | Gly | Trp | Gly 255 | Gly |
| Leu | Phe | Cys | Asp 260 | Gln | Asp | Leu | Asn | Tyr 265 | Cys | Thr | His | His | Ser 270 | Pro | Cys |
| Lys | Asn | Gly 275 | Ser | Thr | Cys | Ser | Asn 280 | Ser | Gly | Pro | Lys | Gly 285 | Tyr | Thr | Cys |
| Thr | Cys 290 | Leu | Pro | Gly | Tyr | Thr 295 | Gly | Glu | His | Cys | Glu 300 | Leu | Gly | Leu | Ser |
| Lys 305 | Cys | Ala | Ser | Asn | Pro 310 | Cys | Arg | Asn | Gly | Gly 315 | Ser | Cys | Lys | Asp | Gln 320 |
| Glu | Asn | Ser | Tyr | His 325 | Cys | Leu | Cys | Pro | Pro 330 | Gly | Tyr | Tyr | Gly | Gln 335 | His |
| Cys | Glu | His | Ser 340 | Thr | Leu | Thr | Cys | Ala 345 | Asp | Ser | Pro | Cys | Phe 350 | Asn | Gly |
| Gly | Ser | Cys 355 | Arg | Glu | Arg | Asn | Gln 360 | Gly | Ser | Ser | Tyr | Ala 365 | Cys | Glu | Cys |
| Pro | Pro 370 | Asn | Phe | Thr | Gly | Ser 375 | Asn | Cys | Glu | Lys | Lys 380 | Val | Asp | Arg | Cys |
| Thr 385 | Ser | Asn | Pro | Cys | Ala 390 | Asn | Gly | Gly | Gln | Cys 395 | Leu | Asn | Arg | Gly | Pro 400 |
| Ser | Arg | Thr | Cys | Arg 405 | Cys | Arg | Pro | Gly | Phe 410 | Thr | Gly | Thr | His | Cys 415 | Glu |

Leu His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr
 420 425 430
 Cys His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe
 435 440 445
 Ser Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser
 450 455 460
 Gly Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn
 465 470 475 480
 Asn Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu
 485 490 495
 Phe Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu
 500 505 510
 Gly Val Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val
 515 520 525
 Ala Val Arg Gln Leu Arg Leu Arg Arg Pro Asp Asp Glu Ser Arg Glu
 530 535 540
 Ala Met Asn Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala
 545 550 555 560
 Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys
 565 570 575
 Gly Leu Asp Lys Ser Asn Cys Gly Lys Leu Gln Asn His Thr Leu Asp
 580 585 590
 Tyr Asn Leu Ala Pro Gly Leu Leu Gly Arg Gly Ser Met Pro Gly Lys
 595 600 605
 Tyr Pro His Ser Asp Lys Ser Leu Gly Glu Lys Val Pro Leu Arg Leu
 610 615 620
 His Ser Glu Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg
 625 630 635 640
 Asp Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu
 645 650 655
 Cys Val Ile Ala Thr Glu Val
 660

<210> 19

<211> 662

<212> PRT

<213> Murine

<220>

<223> Murine protein sequence (less signal sequence)

<400> 19

Ala Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn
 1 5 10 15
 Gln Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg
 20 25 30

Thr Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu
 35 40 45
 Gly Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn
 50 55 60
 Ser Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu
 65 70 75 80
 Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile
 85 90 95
 Gln Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro
 100 105 110
 Gly Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val
 115 120 125
 Gly Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu
 130 135 140
 Ser Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser
 145 150 155 160
 Cys Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu
 165 170 175
 Cys Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys
 180 185 190
 Tyr Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly
 195 200 205
 Tyr Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly
 210 215 220
 Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr
 225 230 235 240
 Cys Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu
 245 250 255
 Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys
 260 265 270
 Asn Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr
 275 280 285
 Cys Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys
 290 295 300
 Cys Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu
 305 310 315 320
 Asn Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys
 325 330 335
 Glu His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly
 340 345 350
 Ser Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro
 355 360 365

Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr
 370 375 380
 Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser
 385 390 395 400
 Arg Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu
 405 410 415
 His Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys
 420 425 430
 His Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser
 435 440 445
 Gly Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly
 450 455 460
 Pro Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn
 465 470 475 480
 Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe
 485 490 495
 Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly
 500 505 510
 Val Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala
 515 520 525
 Val Arg Gln Leu Arg Leu Arg Arg Pro Asp Asp Glu Ser Arg Glu Ala
 530 535 540
 Met Asn Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala
 545 550 555 560
 Gln Leu Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly
 565 570 575
 Leu Asp Lys Ser Asn Cys Gly Lys Leu Gln Asn His Thr Leu Asp Tyr
 580 585 590
 Asn Leu Ala Pro Gly Leu Leu Gly Arg Gly Ser Met Pro Gly Lys Tyr
 595 600 605
 Pro His Ser Asp Lys Ser Leu Gly Glu Lys Val Pro Leu Arg Leu His
 610 615 620
 Ser Glu Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp
 625 630 635 640
 Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu Cys
 645 650 655
 Val Ile Ala Thr Glu Val
 660

<210> 20
 <211> 661
 <212> PRT
 <213> Murine

<220>
 <223> Murine protein sequence (less signal sequence)

<400> 20

Ala Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln
 1 5 10 15
 Arg Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr
 20 25 30
 Phe Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly
 35 40 45
 Pro Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser
 50 55 60
 Phe Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln
 65 70 75 80
 Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln
 85 90 95
 Ala Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly
 100 105 110
 Asn Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly
 115 120 125
 Lys Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser
 130 135 140
 Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys
 145 150 155 160
 Ser Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys
 165 170 175
 Gln Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr
 180 185 190
 Cys Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr
 195 200 205
 Cys Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg
 210 215 220
 Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys
 225 230 235 240
 Ser Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe
 245 250 255
 Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn
 260 265 270
 Gly Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys
 275 280 285

Leu Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys
 290 295 300
 Ala Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn
 305 310 315 320
 Ser Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu
 325 330 335
 His Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser
 340 345 350
 Cys Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro
 355 360 365
 Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser
 370 375 380
 Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg
 385 390 395 400
 Thr Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His
 405 410 415
 Ile Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His
 420 425 430
 Asp Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly
 435 440 445
 Arg Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro
 450 455 460
 Cys Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe
 465 470 475 480
 Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro
 485 490 495
 Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val
 500 505 510
 Gly Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala Val
 515 520 525
 Arg Gln Leu Arg Leu Arg Arg Pro Asp Asp Glu Ser Arg Glu Ala Met
 530 535 540
 Asn Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln
 545 550 555 560
 Leu Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu
 565 570 575
 Asp Lys Ser Asn Cys Gly Lys Leu Gln Asn His Thr Leu Asp Tyr Asn
 580 585 590
 Leu Ala Pro Gly Leu Leu Gly Arg Gly Ser Met Pro Gly Lys Tyr Pro
 595 600 605
 His Ser Asp Lys Ser Leu Gly Glu Lys Val Pro Leu Arg Leu His Ser
 610 615 620

Glu Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser
625 630 635 640

Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu Cys Val
645 650 655

Ile Ala Thr Glu Val
660

<210> 21

<211> 660

<212> PRT

<213> Murine

<220>

<223> Murine protein sequence (less signal sequence)

<400> 21

Gly Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln Arg
1 5 10 15

Gly Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe
20 25 30

Phe Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly Pro
35 40 45

Cys Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe
50 55 60

Val Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu
65 70 75 80

Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala
85 90 95

Trp His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn
100 105 110

Ser Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly Lys
115 120 125

Ile Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr
130 135 140

Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser
145 150 155 160

Arg Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln
165 170 175

Pro Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys
180 185 190

Asp Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys
195 200 205

Ser Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu
210 215 220

Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser
225 230 235 240

Ile Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys
 245 250 255
 Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly
 260 265 270
 Ser Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu
 275 280 285
 Pro Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys Ala
 290 295 300
 Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser
 305 310 315 320
 Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu His
 325 330 335
 Ser Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys
 340 345 350
 Arg Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn
 355 360 365
 Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn
 370 375 380
 Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr
 385 390 395 400
 Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His Ile
 405 410 415
 Ser Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His Asp
 420 425 430
 Leu Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg
 435 440 445
 Arg Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro Cys
 450 455 460
 Phe Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val
 465 470 475 480
 Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val
 485 490 495
 Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly
 500 505 510
 Leu Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala Val Arg
 515 520 525
 Gln Leu Arg Leu Arg Arg Pro Asp Asp Glu Ser Arg Glu Ala Met Asn
 530 535 540
 Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu
 545 550 555 560
 Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu Asp
 565 570 575

Lys Ser Asn Cys Gly Lys Leu Gln Asn His Thr Leu Asp Tyr Asn Leu
 580 585 590
 Ala Pro Gly Leu Leu Gly Arg Gly Ser Met Pro Gly Lys Tyr Pro His
 595 600 605
 Ser Asp Lys Ser Leu Gly Glu Lys Val Pro Leu Arg Leu His Ser Glu
 610 615 620
 Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser Met
 625 630 635 640
 Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu Cys Val Ile
 645 650 655
 Ala Thr Glu Val
 660

<210> 22
 <211> 659
 <212> PRT
 <213> Murine

<220>
 <223> Murine protein sequence (less signal sequence)

<400> 22

Ser Gly Ile Phe Gln Leu Arg Leu Gln Glu Phe Val Asn Gln Arg Gly
 1 5 10 15
 Met Leu Ala Asn Gly Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe Phe
 20 25 30
 Arg Ile Cys Leu Lys His Phe Gln Ala Thr Phe Ser Glu Gly Pro Cys
 35 40 45
 Thr Phe Gly Asn Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Val
 50 55 60
 Val Arg Asp Lys Asn Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu Pro
 65 70 75 80
 Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala Trp
 85 90 95
 His Thr Pro Gly Asp Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn Ser
 100 105 110
 Leu Ile Ser Gln Ile Ile Ile Gln Gly Ser Leu Ala Val Gly Lys Ile
 115 120 125
 Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr Ser
 130 135 140
 Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser Arg
 145 150 155 160
 Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln Pro
 165 170 175
 Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys Asp
 180 185 190

Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser
 195 200 205
 Lys Pro Asp Glu Cys Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys
 210 215 220
 Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Ile
 225 230 235 240
 Pro Trp Gln Cys Ala Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp
 245 250 255
 Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ser
 260 265 270
 Thr Cys Ser Asn Ser Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu Pro
 275 280 285
 Gly Tyr Thr Gly Glu His Cys Glu Leu Gly Leu Ser Lys Cys Ala Ser
 290 295 300
 Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser Tyr
 305 310 315 320
 His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Gln His Cys Glu His Ser
 325 330 335
 Thr Leu Thr Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg
 340 345 350
 Glu Arg Asn Gln Gly Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn Phe
 355 360 365
 Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro
 370 375 380
 Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr Cys
 385 390 395 400
 Arg Cys Arg Pro Gly Phe Thr Gly Thr His Cys Glu Leu His Ile Ser
 405 410 415
 Asp Cys Ala Arg Ser Pro Cys Ala His Gly Gly Thr Cys His Asp Leu
 420 425 430
 Glu Asn Gly Pro Val Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg
 435 440 445
 Cys Glu Val Arg Ile Thr His Asp Ala Cys Ala Ser Gly Pro Cys Phe
 450 455 460
 Asn Gly Ala Thr Cys Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val Cys
 465 470 475 480
 Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly
 485 490 495
 Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu
 500 505 510
 Val Val Leu Leu Val Leu Leu Val Met Val Val Val Ala Val Arg Gln
 515 520 525

Leu Arg Leu Arg Arg Pro Asp Asp Glu Ser Arg Glu Ala Met Asn Asn
 530 535 540
 Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys
 545 550 555 560
 Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu Asp Lys
 565 570 575
 Ser Asn Cys Gly Lys Leu Gln Asn His Thr Leu Asp Tyr Asn Leu Ala
 580 585 590
 Pro Gly Leu Leu Gly Arg Gly Ser Met Pro Gly Lys Tyr Pro His Ser
 595 600 605
 Asp Lys Ser Leu Gly Glu Lys Val Pro Leu Arg Leu His Ser Glu Lys
 610 615 620
 Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr
 625 630 635 640
 Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu Cys Val Ile Ala
 645 650 655
 Thr Glu Val

<210> 23
 <211> 508
 <212> PRT
 <213> Human

<400> 23

Ala Ala Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn
 1 5 10 15
 Glu Arg Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg
 20 25 30
 Thr Phe Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro
 35 40 45
 Gly Pro Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn
 50 55 60
 Ser Phe Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu
 65 70 75 80
 Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile
 85 90 95
 Glu Ala Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro
 100 105 110
 Pro Asp Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val
 115 120 125
 Gly Gln Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu
 130 135 140
 Arg Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn
 145 150 155 160

Cys Ser Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val
 165 170 175
 Cys Gln Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu
 180 185 190
 Tyr Cys Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly
 195 200 205
 Tyr Cys Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly
 210 215 220
 Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr
 225 230 235 240
 Cys Ser Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu
 245 250 255
 Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys
 260 265 270
 Asn Gly Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr
 275 280 285
 Cys Arg Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu
 290 295 300
 Cys Asp Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu
 305 310 315 320
 Asp Gly Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys
 325 330 335
 Glu His Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly
 340 345 350
 Ser Cys Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro
 355 360 365
 Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr
 370 375 380
 Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser
 385 390 395 400
 Arg Met Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu
 405 410 415
 His Val Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys
 420 425 430
 His Asp Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser
 435 440 445
 Gly Arg Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser
 450 455 460
 Pro Cys Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr
 465 470 475 480
 Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe
 485 490 495

Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 24
 <211> 507
 <212> PRT
 <213> Human

<400> 24

Ala Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu
 1 5 10 15
 Arg Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr
 20 25 30
 Phe Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly
 35 40 45
 Pro Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser
 50 55 60
 Phe Ala Val Arg Asp Asp Ser Ser Gly Gly Arg Asn Pro Leu Gln
 65 70 75 80
 Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu
 85 90 95
 Ala Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro
 100 105 110
 Asp Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly
 115 120 125
 Gln Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg
 130 135 140
 Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys
 145 150 155 160
 Ser Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys
 165 170 175
 Gln Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr
 180 185 190
 Cys Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr
 195 200 205
 Cys Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg
 210 215 220
 Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys
 225 230 235 240
 Ser Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe
 245 250 255
 Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn
 260 265 270
 Gly Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys
 275 280 285

Arg Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys
 290 295 300
 Asp Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp
 305 310 315 320
 Gly Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu
 325 330 335
 His Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser
 340 345 350
 Cys Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro
 355 360 365
 Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser
 370 375 380
 Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg
 385 390 395 400
 Met Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His
 405 410 415
 Val Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His
 420 425 430
 Asp Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly
 435 440 445
 Arg Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro
 450 455 460
 Cys Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe
 465 470 475 480
 Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro
 485 490 495
 Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 25
 <211> 506
 <212> PRT
 <213> Human

<400> 25

Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg
 1 5 10 15
 Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe
 20 25 30
 Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro
 35 40 45
 Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe
 50 55 60

Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu
 65 70 75 80
 Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala
 85 90 95
 Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp
 100 105 110
 Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln
 115 120 125
 Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr
 130 135 140
 Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser
 145 150 155 160
 Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln
 165 170 175
 Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys
 180 185 190
 Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys
 195 200 205
 Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu
 210 215 220
 Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser
 225 230 235 240
 Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys
 245 250 255
 Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly
 260 265 270
 Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg
 275 280 285
 Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp
 290 295 300
 Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly
 305 310 315 320
 Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His
 325 330 335
 Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys
 340 345 350
 Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn
 355 360 365
 Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn
 370 375 380
 Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met
 385 390 395 400

Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val
 405 410 415
 Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp
 420 425 430
 Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg
 435 440 445
 Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys
 450 455 460
 Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val
 465 470 475 480
 Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val
 485 490 495
 Gly Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 26
 <211> 505
 <212> PRT
 <213> Human

<400> 26

Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly
 1 5 10 15
 Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe
 20 25 30
 Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys
 35 40 45
 Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala
 50 55 60
 Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro
 65 70 75 80
 Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp
 85 90 95
 His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala
 100 105 110
 Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn
 115 120 125
 Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser
 130 135 140
 Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg
 145 150 155 160
 Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro
 165 170 175
 Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln
 180 185 190

Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser
 195 200 205
 Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys
 210 215 220
 Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr
 225 230 235 240
 Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp
 245 250 255
 Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala
 260 265 270
 Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro
 275 280 285
 Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser
 290 295 300
 Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr
 305 310 315 320
 His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser
 325 330 335
 Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg
 340 345 350
 Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe
 355 360 365
 Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro
 370 375 380
 Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys
 385 390 395 400
 Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser
 405 410 415
 Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu
 420 425 430
 Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg
 435 440 445
 Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe
 450 455 460
 Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys
 465 470 475 480
 Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly
 485 490 495
 Leu Pro Pro Ser Phe Pro Trp Val Ala
 500 505

<210> 27
 <211> 504
 <212> PRT
 <213> Human

<400> 27

Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val
 1 5 10 15
 Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg
 20 25 30
 Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr
 35 40 45
 Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val
 50 55 60
 Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe
 65 70 75 80
 Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His
 85 90 95
 Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu
 100 105 110
 Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp
 115 120 125
 Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr
 130 135 140
 Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu
 145 150 155 160
 Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro Asp
 165 170 175
 Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln
 180 185 190
 Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys
 195 200 205
 Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn
 210 215 220
 Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro
 225 230 235 240
 Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln
 245 250 255
 Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala Thr
 260 265 270
 Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly
 275 280 285
 Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn
 290 295 300

Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His
 305 310 315 320
 Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr
 325 330 335
 Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu
 340 345 350
 Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr
 355 360 365
 Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys
 370 375 380
 Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg
 385 390 395 400
 Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp
 405 410 415
 Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu
 420 425 430
 Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys
 435 440 445
 Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn
 450 455 460
 Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn
 465 470 475 480
 Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu
 485 490 495
 Pro Pro Ser Phe Pro Trp Val Ala
 500

<210> 28
 <211> 503
 <212> PRT
 <213> Human

<400> 28

Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu
 1 5 10 15
 Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val
 20 25 30
 Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe
 35 40 45
 Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg
 50 55 60
 Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn
 65 70 75 80
 Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala
 85 90 95

Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile
 100 105 110
 Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu
 115 120 125
 Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg
 130 135 140
 Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys
 145 150 155 160
 Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly
 165 170 175
 Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro
 180 185 190
 Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro
 195 200 205
 Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu
 210 215 220
 Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp
 225 230 235 240
 Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp
 245 250 255
 Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys
 260 265 270
 Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr
 275 280 285
 Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro
 290 295 300
 Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys
 305 310 315 320
 Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu
 325 330 335
 Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg
 340 345 350
 Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly
 355 360 365
 Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala
 370 375 380
 Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys
 385 390 395 400
 Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys
 405 410 415
 Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn
 420 425 430

Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu
 435 440 445
 Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg
 450 455 460
 Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys
 465 470 475 480
 Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro
 485 490 495
 Pro Ser Phe Pro Trp Val Ala
 500

<210> 29
 <211> 529
 <212> PRT
 <213> Human

<220>
 <223> Human protein sequence (less signal sequence and
 intracellular domain)

<400> 29

Ala Ala Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn
 1 5 10 15
 Glu Arg Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg
 20 25 30
 Thr Phe Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro
 35 40 45
 Gly Pro Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn
 50 55 60
 Ser Phe Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu
 65 70 75 80
 Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile
 85 90 95
 Glu Ala Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro
 100 105 110
 Pro Asp Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val
 115 120 125
 Gly Gln Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu
 130 135 140
 Arg Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn
 145 150 155 160
 Cys Ser Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val
 165 170 175
 Cys Gln Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu
 180 185 190

Tyr Cys Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly
 195 200 205
 Tyr Cys Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly
 210 215 220
 Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr
 225 230 235 240
 Cys Ser Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu
 245 250 255
 Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys
 260 265 270
 Asn Gly Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr
 275 280 285
 Cys Arg Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu
 290 295 300
 Cys Asp Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu
 305 310 315 320
 Asp Gly Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys
 325 330 335
 Glu His Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly
 340 345 350
 Ser Cys Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro
 355 360 365
 Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr
 370 375 380
 Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser
 385 390 395 400
 Arg Met Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu
 405 410 415
 His Val Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys
 420 425 430
 His Asp Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser
 435 440 445
 Gly Arg Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser
 450 455 460
 Pro Cys Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr
 465 470 475 480
 Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe
 485 490 495
 Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly
 500 505 510
 Val Gly Leu Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala
 515 520 525
 Val

<210> 30
 <211> 528
 <212> PRT
 <213> Human

<220>
 <223> Human protein sequence (less signal sequence and
 intracellular domain)

<400> 30

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Ala Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu
 1           5           10           15
Arg Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr
          20           25           30
Phe Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly
          35           40           45
Pro Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser
          50           55           60
Phe Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln
          65           70           75           80
Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu
          85           90           95
Ala Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro
          100          105          110
Asp Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly
          115          120          125
Gln Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg
          130          135          140
Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys
          145          150          155          160
Ser Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys
          165          170          175
Gln Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr
          180          185          190
Cys Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr
          195          200          205
Cys Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg
          210          215          220
Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys
          225          230          235          240
Ser Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe
          245          250          255
Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn
          260          265          270

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Gly Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys
 275 280 285
 Arg Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys
 290 300
 Asp Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp
 305 310 315 320
 Gly Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu
 325 330 335
 His Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser
 340 345 350
 Cys Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro
 355 360 365
 Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser
 370 375 380
 Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg
 385 390 395 400
 Met Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His
 405 410 415
 Val Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His
 420 425 430
 Asp Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly
 435 440 445
 Arg Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro
 450 455 460
 Cys Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe
 465 470 475 480
 Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro
 485 490 495
 Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val
 500 505 510
 Gly Leu Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val
 515 520 525

<210> 31

<211> 527

<212> PRT

<213> Human

<220>

 <223> Human protein sequence (less signal sequence and
 intracellular domain)

<400> 31

Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg
 1 5 10 15
 Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe
 20 25 30
 Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro
 35 40 45
 Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe
 50 55 60
 Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu
 65 70 75 80
 Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala
 85 90 95
 Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp
 100 105 110
 Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln
 115 120 125
 Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr
 130 135 140
 Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser
 145 150 155 160
 Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln
 165 170 175
 Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys
 180 185 190
 Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys
 195 200 205
 Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu
 210 215 220
 Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser
 225 230 235 240
 Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys
 245 250 255
 Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly
 260 265 270
 Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg
 275 280 285
 Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp
 290 295 300
 Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly
 305 310 315 320
 Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His
 325 330 335

Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys
 340 345 350
 Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn
 355 360 365
 Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn
 370 375 380
 Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met
 385 390 395 400
 Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val
 405 410 415
 Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp
 420 425 430
 Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg
 435 440 445
 Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys
 450 455 460
 Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val
 465 470 475 480
 Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val
 485 490 495
 Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly
 500 505 510
 Leu Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val
 515 520 525

<210> 32

<211> 526

<212> PRT

<213> Human

<220>

 <223> Human protein sequence (less signal sequence and
 intracellular domain)

<400> 32

Ser Gly Val Phe Gln Leu Gln Leu Glu Phe Ile Asn Glu Arg Gly
 1 5 10 15
 Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe
 20 25 30
 Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys
 35 40 45
 Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala
 50 55 60
 Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro
 65 70 75 80

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Asn | Phe | Thr | Trp | Pro | Gly | Thr | Phe | Ser | Leu | Ile | Ile | Glu | Ala | Trp |
| | | | | 85 | | | | | 90 | | | | | | 95 |
| His | Ala | Pro | Gly | Asp | Asp | Leu | Arg | Pro | Glu | Ala | Leu | Pro | Pro | Asp | Ala |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Leu | Ile | Ser | Lys | Ile | Ala | Ile | Gln | Gly | Ser | Leu | Ala | Val | Gly | Gln | Asn |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Trp | Leu | Leu | Asp | Glu | Gln | Thr | Ser | Thr | Leu | Thr | Arg | Leu | Arg | Tyr | Ser |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Tyr | Arg | Val | Ile | Cys | Ser | Asp | Asn | Tyr | Tyr | Gly | Asp | Asn | Cys | Ser | Arg |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Leu | Cys | Lys | Lys | Arg | Asn | Asp | His | Phe | Gly | His | Tyr | Val | Cys | Gln | Pro |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Asp | Gly | Asn | Leu | Ser | Cys | Leu | Pro | Gly | Trp | Thr | Gly | Glu | Tyr | Cys | Gln |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Gln | Pro | Ile | Cys | Leu | Ser | Gly | Cys | His | Glu | Gln | Asn | Gly | Tyr | Cys | Ser |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Lys | Pro | Ala | Glu | Cys | Leu | Cys | Arg | Pro | Gly | Trp | Gln | Gly | Arg | Leu | Cys |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Asn | Glu | Cys | Ile | Pro | His | Asn | Gly | Cys | Arg | His | Gly | Thr | Cys | Ser | Thr |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Pro | Trp | Gln | Cys | Thr | Cys | Asp | Glu | Gly | Trp | Gly | Gly | Leu | Phe | Cys | Asp |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Gln | Asp | Leu | Asn | Tyr | Cys | Thr | His | His | Ser | Pro | Cys | Lys | Asn | Gly | Ala |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Thr | Cys | Ser | Asn | Ser | Gly | Gln | Arg | Ser | Tyr | Thr | Cys | Thr | Cys | Arg | Pro |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Gly | Tyr | Thr | Gly | Val | Asp | Cys | Glu | Leu | Glu | Leu | Ser | Glu | Cys | Asp | Ser |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Asn | Pro | Cys | Arg | Asn | Gly | Gly | Ser | Cys | Lys | Asp | Gln | Glu | Asp | Gly | Tyr |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| His | Cys | Leu | Cys | Pro | Pro | Gly | Tyr | Tyr | Gly | Leu | His | Cys | Glu | His | Ser |
| | | | | 325 | | | | | 330 | | | | | 335 | |
| Thr | Leu | Ser | Cys | Ala | Asp | Ser | Pro | Cys | Phe | Asn | Gly | Gly | Ser | Cys | Arg |
| | | | 340 | | | | | 345 | | | | | 350 | | |
| Glu | Arg | Asn | Gln | Gly | Ala | Asn | Tyr | Ala | Cys | Glu | Cys | Pro | Pro | Asn | Phe |
| | | 355 | | | | | 360 | | | | | 365 | | | |
| Thr | Gly | Ser | Asn | Cys | Glu | Lys | Lys | Val | Asp | Arg | Cys | Thr | Ser | Asn | Pro |
| | 370 | | | | | 375 | | | | | 380 | | | | |
| Cys | Ala | Asn | Gly | Gly | Gln | Cys | Leu | Asn | Arg | Gly | Pro | Ser | Arg | Met | Cys |
| 385 | | | | | 390 | | | | | 395 | | | | | 400 |
| Arg | Cys | Arg | Pro | Gly | Phe | Thr | Gly | Thr | Tyr | Cys | Glu | Leu | His | Val | Ser |
| | | | | 405 | | | | | 410 | | | | | 415 | |

Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu
 420 425 430
 Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg
 435 440 445
 Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe
 450 455 460
 Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys
 465 470 475 480
 Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly
 485 490 495
 Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu
 500 505 510
 Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val
 515 520 525

<210> 33

<211> 525

<212> PRT

<213> Human

<220>

<223> Human protein sequence (less signal sequence and
intracellular domain)

<400> 33

Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val
 1 5 10 15
 Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg
 20 25 30
 Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr
 35 40 45
 Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val
 50 55 60
 Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe
 65 70 75 80
 Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His
 85 90 95
 Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu
 100 105 110
 Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp
 115 120 125
 Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr
 130 135 140
 Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu
 145 150 155 160

Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro Asp
 165 170 175
 Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln
 180 185 190
 Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys
 195 200 205
 Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn
 210 215 220
 Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro
 225 230 235 240
 Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln
 245 250 255
 Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala Thr
 260 265 270
 Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly
 275 280 285
 Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn
 290 295 300
 Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His
 305 310 315 320
 Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr
 325 330 335
 Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu
 340 345 350
 Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr
 355 360 365
 Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys
 370 375 380
 Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg
 385 390 395 400
 Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp
 405 410 415
 Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu
 420 425 430
 Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys
 435 440 445
 Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn
 450 455 460
 Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn
 465 470 475 480
 Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu
 485 490 495

Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala
 500 505 510

Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val
 515 520 525

<210> 34
 <211> 524
 <212> PRT
 <213> Human

<220>
 <223> Human protein sequence (less signal sequence and
 intracellular domain)

<400> 34

Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu
 1 5 10 15

Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val
 20 25 30

Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe
 35 40 45

Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg
 50 55 60

Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn
 65 70 75 80

Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala
 85 90 95

Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile
 100 105 110

Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu
 115 120 125

Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg
 130 135 140

Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys
 145 150 155 160

Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly
 165 170 175

Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro
 180 185 190

Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro
 195 200 205

Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu
 210 215 220

Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp
 225 230 235 240

Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp
 245 250 255
 Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys
 260 265 270
 Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr
 275 280 285
 Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro
 290 295 300
 Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys
 305 310 315 320
 Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu
 325 330 335
 Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg
 340 345 350
 Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly
 355 360 365
 Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala
 370 375 380
 Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys
 385 390 395 400
 Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys
 405 410 415
 Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn
 420 425 430
 Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu
 435 440 445
 Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg
 450 455 460
 Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys
 465 470 475 480
 Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro
 485 490 495
 Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala Val
 500 505 510
 Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val
 515 520

<210> 35

<211> 682

<212> PRT

<213> Human

<220>

<223> Human protein sequence (less signal sequence)

<400> 35

Ala Ala Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn
 1 5 10 15
 Glu Arg Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg
 20 25 30
 Thr Phe Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro
 35 40 45
 Gly Pro Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn
 50 55 60
 Ser Phe Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu
 65 70 75 80
 Gln Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile
 85 90 95
 Glu Ala Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro
 100 105 110
 Pro Asp Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val
 115 120 125
 Gly Gln Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu
 130 135 140
 Arg Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn
 145 150 155 160
 Cys Ser Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val
 165 170 175
 Cys Gln Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu
 180 185 190
 Tyr Cys Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly
 195 200 205
 Tyr Cys Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly
 210 215 220
 Arg Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr
 225 230 235 240
 Cys Ser Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu
 245 250 255
 Phe Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys
 260 265 270
 Asn Gly Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr
 275 280 285
 Cys Arg Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu
 290 295 300
 Cys Asp Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu
 305 310 315 320
 Asp Gly Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys
 325 330 335

Glu His Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly
 340 345 350
 Ser Cys Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro
 355 360 365
 Pro Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr
 370 375 380
 Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser
 385 390 395 400
 Arg Met Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu
 405 410 415
 His Val Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys
 420 425 430
 His Asp Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser
 435 440 445
 Gly Arg Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser
 450 455 460
 Pro Cys Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr
 465 470 475 480
 Phe Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe
 485 490 495
 Pro Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly
 500 505 510
 Val Gly Leu Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala
 515 520 525
 Val Arg Gln Leu Arg Leu Arg Arg Pro Asp Asp Gly Ser Arg Glu Ala
 530 535 540
 Met Asn Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala
 545 550 555 560
 Gln Leu Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly
 565 570 575
 Leu Asp Lys Ser Asn Cys Gly Lys Gln Gln Asn His Thr Leu Asp Tyr
 580 585 590
 Asn Leu Ala Pro Gly Pro Leu Gly Arg Gly Thr Met Pro Gly Lys Phe
 595 600 605
 Pro His Ser Asp Lys Ser Leu Gly Glu Lys Ala Pro Leu Arg Leu His
 610 615 620
 Ser Glu Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp
 625 630 635 640
 Ser Met Tyr Gln Ser Val Cys Pro Glu Cys Arg Ile Ser Ala Ile Cys
 645 650 655
 Ser Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu
 660 665 670

Arg Asn Glu Cys Val Ile Ala Thr Glu Val
675 680

<210> 36

<211> 681

<212> PRT

<213> Human

<220>

<223> Human protein sequence (less signal sequence)

<400> 36

Ala Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu
1 5 10 15
Arg Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr
20 25 30
Phe Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly
35 40 45
Pro Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser
50 55 60
Phe Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln
65 70 75 80
Leu Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu
85 90 95
Ala Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro
100 105 110
Asp Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly
115 120 125
Gln Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg
130 135 140
Tyr Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys
145 150 155 160
Ser Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys
165 170 175
Gln Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr
180 185 190
Cys Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr
195 200 205
Cys Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg
210 215 220
Leu Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys
225 230 235 240
Ser Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe
245 250 255
Cys Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn
260 265 270

Gly Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys
 275 280 285
 Arg Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys
 290 295 300
 Asp Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp
 305 310 315 320
 Gly Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu
 325 330 335
 His Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser
 340 345 350
 Cys Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro
 355 360 365
 Asn Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser
 370 375 380
 Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg
 385 390 395 400
 Met Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His
 405 410 415
 Val Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His
 420 425 430
 Asp Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly
 435 440 445
 Arg Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro
 450 455 460
 Cys Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe
 465 470 475 480
 Val Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro
 485 490 495
 Val Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val
 500 505 510
 Gly Leu Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val
 515 520 525
 Arg Gln Leu Arg Leu Arg Arg Pro Asp Asp Gly Ser Arg Glu Ala Met
 530 535 540
 Asn Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln
 545 550 555 560
 Leu Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu
 565 570 575
 Asp Lys Ser Asn Cys Gly Lys Gln Gln Asn His Thr Leu Asp Tyr Asn
 580 585 590
 Leu Ala Pro Gly Pro Leu Gly Arg Gly Thr Met Pro Gly Lys Phe Pro
 595 600 605

His Ser Asp Lys Ser Leu Gly Glu Lys Ala Pro Leu Arg Leu His Ser
 610 615 620
 Glu Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser
 625 630 635 640
 Met Tyr Gln Ser Val Cys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser
 645 650 655
 Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg
 660 665 670
 Asn Glu Cys Val Ile Ala Thr Glu Val
 675 680

<210> 37
 <211> 680
 <212> PRT
 <213> Human

<220>
 <223> Human protein sequence (less signal sequence)

<400> 37

Gly Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg
 1 5 10 15
 Gly Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe
 20 25 30
 Phe Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro
 35 40 45
 Cys Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe
 50 55 60
 Ala Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu
 65 70 75 80
 Pro Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala
 85 90 95
 Trp His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp
 100 105 110
 Ala Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln
 115 120 125
 Asn Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr
 130 135 140
 Ser Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser
 145 150 155 160
 Arg Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln
 165 170 175
 Pro Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys
 180 185 190
 Gln Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys
 195 200 205

Ser Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu
 210 215 220
 Cys Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser
 225 230 235 240
 Thr Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys
 245 250 255
 Asp Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly
 260 265 270
 Ala Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg
 275 280 285
 Pro Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp
 290 295 300
 Ser Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly
 305 310 315 320
 Tyr His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His
 325 330 335
 Ser Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys
 340 345 350
 Arg Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn
 355 360 365
 Phe Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn
 370 375 380
 Pro Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met
 385 390 395 400
 Cys Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val
 405 410 415
 Ser Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp
 420 425 430
 Leu Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg
 435 440 445
 Arg Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys
 450 455 460
 Phe Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val
 465 470 475 480
 Cys Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val
 485 490 495
 Gly Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly
 500 505 510
 Leu Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val Arg
 515 520 525
 Gln Leu Arg Leu Arg Arg Pro Asp Asp Gly Ser Arg Glu Ala Met Asn
 530 535 540

Asn Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu
 545 550 555 560
 Lys Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu Asp
 565 570 575
 Lys Ser Asn Cys Gly Lys Gln Gln Asn His Thr Leu Asp Tyr Asn Leu
 580 585 590
 Ala Pro Gly Pro Leu Gly Arg Gly Thr Met Pro Gly Lys Phe Pro His
 595 600 605
 Ser Asp Lys Ser Leu Gly Glu Lys Ala Pro Leu Arg Leu His Ser Glu
 610 615 620
 Lys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser Met
 625 630 635 640
 Tyr Gln Ser Val Cys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro
 645 650 655
 Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn
 660 665 670
 Glu Cys Val Ile Ala Thr Glu Val
 675 680

<210> 38
 <211> 679
 <212> PRT
 <213> Human

<220>
 <223> Human protein sequence (less signal sequence)

<400> 38

Ser Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly
 1 5 10 15
 Val Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe
 20 25 30
 Arg Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys
 35 40 45
 Thr Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala
 50 55 60
 Val Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro
 65 70 75 80
 Phe Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp
 85 90 95
 His Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala
 100 105 110
 Leu Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn
 115 120 125
 Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser
 130 135 140

Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg
 145 150 155 160
 Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro
 165 170 175
 Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln
 180 185 190
 Gln Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser
 195 200 205
 Lys Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys
 210 215 220
 Asn Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr
 225 230 235 240
 Pro Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp
 245 250 255
 Gln Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala
 260 265 270
 Thr Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro
 275 280 285
 Gly Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser
 290 295 300
 Asn Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr
 305 310 315 320
 His Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser
 325 330 335
 Thr Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg
 340 345 350
 Glu Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe
 355 360 365
 Thr Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro
 370 375 380
 Cys Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys
 385 390 395 400
 Arg Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser
 405 410 415
 Asp Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu
 420 425 430
 Glu Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg
 435 440 445
 Cys Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe
 450 455 460
 Asn Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys
 465 470 475 480

Asn Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly
 485 490 495
 Leu Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu
 500 505 510
 Ala Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val Arg Gln
 515 520 525
 Leu Arg Leu Arg Arg Pro Asp Asp Gly Ser Arg Glu Ala Met Asn Asn
 530 535 540
 Leu Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys
 545 550 555 560
 Asn Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu Asp Lys
 565 570 575
 Ser Asn Cys Gly Lys Gln Gln Asn His Thr Leu Asp Tyr Asn Leu Ala
 580 585 590
 Pro Gly Pro Leu Gly Arg Gly Thr Met Pro Gly Lys Phe Pro His Ser
 595 600 605
 Asp Lys Ser Leu Gly Glu Lys Ala Pro Leu Arg Leu His Ser Glu Lys
 610 615 620
 Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr
 625 630 635 640
 Gln Ser Val Cys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg
 645 650 655
 Asp Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu
 660 665 670
 Cys Val Ile Ala Thr Glu Val
 675

<210> 39

<211> 678

<212> PRT

<213> Human

<220>

<223> Human protein sequence (less signal sequence)

<400> 39

Gly Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val
 1 5 10 15
 Leu Ala Ser Gly Arg Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg
 20 25 30
 Val Cys Leu Lys His Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr
 35 40 45
 Phe Gly Thr Val Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val
 50 55 60
 Arg Asp Asp Ser Ser Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe
 65 70 75 80

Asn Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His
 85 90 95
 Ala Pro Gly Asp Asp Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu
 100 105 110
 Ile Ser Lys Ile Ala Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp
 115 120 125
 Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr
 130 135 140
 Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu
 145 150 155 160
 Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro Asp
 165 170 175
 Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln
 180 185 190
 Pro Ile Cys Leu Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys
 195 200 205
 Pro Ala Glu Cys Leu Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn
 210 215 220
 Glu Cys Ile Pro His Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro
 225 230 235 240
 Trp Gln Cys Thr Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln
 245 250 255
 Asp Leu Asn Tyr Cys Thr His His Ser Pro Cys Lys Asn Gly Ala Thr
 260 265 270
 Cys Ser Asn Ser Gly Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly
 275 280 285
 Tyr Thr Gly Val Asp Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn
 290 295 300
 Pro Cys Arg Asn Gly Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His
 305 310 315 320
 Cys Leu Cys Pro Pro Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr
 325 330 335
 Leu Ser Cys Ala Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu
 340 345 350
 Arg Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr
 355 360 365
 Gly Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys
 370 375 380
 Ala Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg
 385 390 395 400
 Cys Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp
 405 410 415

Cys Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu
 420 425 430
 Asn Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys
 435 440 445
 Glu Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn
 450 455 460
 Arg Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn
 465 470 475 480
 Cys Pro Tyr Gly Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu
 485 490 495
 Pro Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala
 500 505 510
 Val Leu Leu Val Leu Leu Gly Met Val Ala Val Ala Val Arg Gln Leu
 515 520 525
 Arg Leu Arg Arg Pro Asp Asp Gly Ser Arg Glu Ala Met Asn Asn Leu
 530 535 540
 Ser Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn
 545 550 555 560
 Thr Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser
 565 570 575
 Asn Cys Gly Lys Gln Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro
 580 585 590
 Gly Pro Leu Gly Arg Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp
 595 600 605
 Lys Ser Leu Gly Glu Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro
 610 615 620
 Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln
 625 630 635 640
 Ser Val Cys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp
 645 650 655
 Ser Met Tyr Gln Ser Val Cys Leu Ile Ser Glu Glu Arg Asn Glu Cys
 660 665 670
 Val Ile Ala Thr Glu Val
 675

<210> 40
 <211> 677
 <212> PRT
 <213> Human

<220>
 <223> Human protein sequence (less signal sequence)

<400> 40

Val Phe Gln Leu Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu
 1 5 10 15

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ser | Gly | Arg | Pro | Cys | Glu | Pro | Gly | Cys | Arg | Thr | Phe | Arg | Val | |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Cys | Leu | Lys | His | Phe | Gln | Ala | Val | Val | Ser | Pro | Gly | Pro | Cys | Thr | Phe |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Gly | Thr | Val | Ser | Thr | Pro | Val | Leu | Gly | Thr | Asn | Ser | Phe | Ala | Val | Arg |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Asp | Asp | Ser | Ser | Gly | Gly | Gly | Arg | Asn | Pro | Leu | Gln | Leu | Pro | Phe | Asn |
| 65 | | | | 70 | | | | | 75 | | | | | | 80 |
| Phe | Thr | Trp | Pro | Gly | Thr | Phe | Ser | Leu | Ile | Ile | Glu | Ala | Trp | His | Ala |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Pro | Gly | Asp | Asp | Leu | Arg | Pro | Glu | Ala | Leu | Pro | Pro | Asp | Ala | Leu | Ile |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Ser | Lys | Ile | Ala | Ile | Gln | Gly | Ser | Leu | Ala | Val | Gly | Gln | Asn | Trp | Leu |
| | | 115 | | | | 120 | | | | | | 125 | | | |
| Leu | Asp | Glu | Gln | Thr | Ser | Thr | Leu | Thr | Arg | Leu | Arg | Tyr | Ser | Tyr | Arg |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Val | Ile | Cys | Ser | Asp | Asn | Tyr | Tyr | Gly | Asp | Asn | Cys | Ser | Arg | Leu | Cys |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Lys | Lys | Arg | Asn | Asp | His | Phe | Gly | His | Tyr | Val | Cys | Gln | Pro | Asp | Gly |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Asn | Leu | Ser | Cys | Leu | Pro | Gly | Trp | Thr | Gly | Glu | Tyr | Cys | Gln | Gln | Pro |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Ile | Cys | Leu | Ser | Gly | Cys | His | Glu | Gln | Asn | Gly | Tyr | Cys | Ser | Lys | Pro |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Ala | Glu | Cys | Leu | Cys | Arg | Pro | Gly | Trp | Gln | Gly | Arg | Leu | Cys | Asn | Glu |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Cys | Ile | Pro | His | Asn | Gly | Cys | Arg | His | Gly | Thr | Cys | Ser | Thr | Pro | Trp |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Gln | Cys | Thr | Cys | Asp | Glu | Gly | Trp | Gly | Gly | Leu | Phe | Cys | Asp | Gln | Asp |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Leu | Asn | Tyr | Cys | Thr | His | His | Ser | Pro | Cys | Lys | Asn | Gly | Ala | Thr | Cys |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Ser | Asn | Ser | Gly | Gln | Arg | Ser | Tyr | Thr | Cys | Thr | Cys | Arg | Pro | Gly | Tyr |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Thr | Gly | Val | Asp | Cys | Glu | Leu | Glu | Leu | Ser | Glu | Cys | Asp | Ser | Asn | Pro |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Cys | Arg | Asn | Gly | Gly | Ser | Cys | Lys | Asp | Gln | Glu | Asp | Gly | Tyr | His | Cys |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| Leu | Cys | Pro | Pro | Gly | Tyr | Tyr | Gly | Leu | His | Cys | Glu | His | Ser | Thr | Leu |
| | | | | 325 | | | | | 330 | | | | | 335 | |
| Ser | Cys | Ala | Asp | Ser | Pro | Cys | Phe | Asn | Gly | Gly | Ser | Cys | Arg | Glu | Arg |
| | | | 340 | | | | | 345 | | | | | 350 | | |

Asn Gln Gly Ala Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly
 355 360 365
 Ser Asn Cys Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala
 370 375 380
 Asn Gly Gly Gln Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys
 385 390 395 400
 Arg Pro Gly Phe Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys
 405 410 415
 Ala Arg Asn Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn
 420 425 430
 Gly Leu Met Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu
 435 440 445
 Val Arg Thr Ser Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg
 450 455 460
 Ala Thr Cys Tyr Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys
 465 470 475 480
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 Pro Ser Phe Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala Val
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 Leu Arg Arg Pro Asp Asp Gly Ser Arg Glu Ala Met Asn Asn Leu Ser
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 Asp Phe Gln Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr
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 Asn Gln Lys Lys Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn
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 Cys Gly Lys Gln Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly
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 Pro Leu Gly Arg Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp Lys
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 Ser Leu Gly Glu Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro Glu
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 Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln Ser
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 Val Cys Pro Glu Cys Arg Ile Ser Ala Ile Cys Ser Pro Arg Asp Ser
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 <213> Murine

<400> 41

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<210> 42
 <211> 25
 <212> DNA
 <213> Murine

<400> 42

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tgctgtgggt aagatttggc gaaca 25
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<210> 43
 <211> 27
 <212> DNA
 <213> Murine

<400> 43

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ccatccta atcagactcact atagggc 27
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<210> 44
 <211> 2718
 <212> DNA
 <213> Murine

<400> 44

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```



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<210> 45
<211> 25
<212> DNA
<213> Murine

<400> 45

ggtgagtccg cacagggtcaa ggtac

25

<210> 46
<211> 25
<212> DNA
<213> Murine

<400> 46

gacagggggtt gctggcacac ttgtt

25

<210> 47
<211> 982
<212> DNA
<213> Murine

<400> 47

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ggacattatg agtgccagcc agatggcagc ctgtcctgcc tgccgggctg gactgggaag 960
tactgtgacc agcctatatg tc 982

<210> 48
<211> 24
<212> DNA
<213> Murine

<400> 48

agccaccatg acgcctgcgt cccg

24

<210> 49
<211> 25
<212> DNA
<213> Murine

<400> 49

tctattatac ctctgtggca atcac

25

<210> 50
<211> 409
<212> DNA
<213> Human

<400> 50

| | | | | | | |
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| ctgccgcca | gcttaaaaac | acaaaccaga | agaaggagct | ggaagtggac | tgtggcctgg | 120 |
| acaagtccaa | ctgtggcaaa | cagcaaaacc | acacattgga | ctataatctg | gccccagggc | 180 |
| ccctggggcg | ggggaccatg | ccaggaaagt | ttccccacag | tgacaagagc | ttaggagaga | 240 |
| aggcgccact | gcggttacac | agtgaaaagc | cagagtntcg | gatatcagcg | atatgctccc | 300 |
| ccagggactc | catgtaccag | tctgtgtgtt | tgatatacaga | ggagaggaat | gaatgtttca | 360 |
| ttgccacgga | ggtataaggc | aggagcctac | ctgggacatc | cctgctcag | | 409 |

<210> 51
<211> 25
<212> DNA
<213> Human

<400> 51

aagaaggagc tggaagtgga ctgtg

25

<210> 52
<211> 25
<212> DNA
<213> Human

<400> 52

atcaaacaca cagactggta catgg

25

<210> 53
<211> 2184
<212> DNA
<213> Human

<400> 53

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| gcgtcctcgg | cgcggtcgcc | gcccagccgt | agtcacctgg | attacctaca | gcggcagctg | 60 |
| cagcggagcc | agcgagaagg | ccaaagggga | gcagcgctcc | gagaggagcg | cctcttttca | 120 |
| gggaccccg | cggctggcgg | acgcgcggga | aagcggcgctc | gcgaacagag | ccagattgag | 180 |


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<210> 54
<211> 22
<212> DNA
<213> Human

<400> 54

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22

<210> 55
<211> 22
<212> DNA
<213> Human

<400> 55

gatgtcccag gtaggtcct gc

22

<210> 56
<211> 349
<212> DNA
<213> Human

<400> 56

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<210> 57
<211> 17
<212> DNA
<213> Murine

<400> 57

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<210> 58
<211> 19
<212> DNA
<213> Murine

<400> 58

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<210> 59
<211> 30
<212> DNA
<213> Murine

<400> 59

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30

<210> 60
<211> 28
<212> DNA
<213> Murine

<400> 60

tcgcggccgc ggggaagctg ggtggcaa

28

<210> 61
<211> 2292
<212> DNA
<213> hybrid

<220>
<223> Hybrid of mouse and human

<400> 61

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| ccgcagcagc | gcgctgcggg | ctccggcatc | ttccagctgc | ggctgcagga | gttcgtcaac | 120 |
| cagcgcggtg | tgctggccaa | tgggcagctc | tgccaaccgg | gctgccggac | tttcttcgc | 180 |
| atgtgcctta | agcacttcca | ggcaaccttc | tccgagggac | cctgcacctt | tggcaatgtc | 240 |
| tccacgcggg | tattgggcac | caactccttc | gtcgtcaggg | acaagaatag | cggcagtggt | 300 |
| cgcaaccctc | tgcagttgcc | cttcaatttc | acctggccgg | gaaccttctc | actcaacatc | 360 |
| caagcttggc | acacaccggg | agacgacctg | cggccagaga | cttcgccagg | aaactctctc | 420 |
| atcagccaaa | tcatcatcca | aggtctctct | gctgtgggta | agatttggcg | aacagacgag | 480 |
| caaaatgaca | ccctcaccag | actgagctac | tcttaccggg | tcatctgcag | tgacaactac | 540 |
| tatggagaga | gctgttctcg | cctatgcaag | aagcgcgatg | accacttcgg | acattatgag | 600 |
| tgccagccag | atggcagcct | gtcctgcctg | cggggctgga | ctgggaagta | ctgtgaccag | 660 |
| cctatatgtc | tttctggctg | tcatgagcag | aatggttact | gcagcaagcc | agatgagtgc | 720 |
| atctgccgtc | caggttggca | gggtgcgctg | tgcaatgaat | gtatccccc | caatggctgt | 780 |
| cgatcatggc | cctgcagcat | cccctggcag | tgtgcctgcg | atgagggatg | gggaggtctg | 840 |
| ttttgtgacc | aagatctcaa | ctactgtact | caccactctc | cgtgcaagaa | tggatcaacg | 900 |


```

tggtccaaca gtggggccaaa ggggtataacc tgcacctgtc tcccaggcta cactgggtgag 960
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tctccgggta aa 2292

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<210> 62

<211> 764

<212> PRT

<213> hybrid

<220>

<223> Hybrid of mouse and human

<400> 62

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Leu Arg Leu Gln Glu Phe Val Asn Gln Arg Gly Met Leu Ala Asn Gly
          35          40          45
Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Ile Cys Leu Lys
          50          55          60
His Phe Gln Ala Thr Phe Ser Glu Gly Pro Cys Thr Phe Gly Asn Val
          65          70          75          80
Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Val Val Arg Asp Lys Asn
          85          90          95
Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp
          100          105          110
Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala Trp His Thr Pro Gly Asp
          115          120          125
Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn Ser Leu Ile Ser Gln Ile
          130          135          140
Ile Ile Gln Gly Ser Leu Ala Val Gly Lys Ile Trp Arg Thr Asp Glu
          145          150          155          160

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Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr Ser Tyr Arg Val Ile Cys
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 Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys Asp Gln Pro Ile Cys Leu
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 Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Asp Glu Cys
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 245 250 255
 His Asn Gly Cys Arg His Gly Thr Cys Ser Ile Pro Trp Gln Cys Ala
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 Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr
 275 280 285
 Cys Thr His His Ser Pro Cys Lys Asn Gly Ser Thr Cys Ser Asn Ser
 290 295 300
 Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu Pro Gly Tyr Thr Gly Glu
 305 310 315 320
 His Cys Glu Leu Gly Leu Ser Lys Cys Ala Ser Asn Pro Cys Arg Asn
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 Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly
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 Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys
 385 390 395 400
 Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly
 405 410 415
 Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr Cys Arg Cys Arg Pro Gly
 420 425 430
 Phe Thr Gly Thr His Cys Glu Leu His Ile Ser Asp Cys Ala Arg Ser
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 Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Pro Val
 450 455 460
 Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu Val Arg Ile
 465 470 475 480
 Thr His Asp Ala Cys Ala Ser Gly Pro Cys Phe Asn Gly Ala Thr Cys
 485 490 495

Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val Cys Asn Cys Pro Tyr Gly
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 515 520 525
 Pro Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
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 Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 545 550 555 560
 Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 565 570 575
 Thr Cys Val Val Val Asp Val Ser His Lys Asn Pro Glu Val Asn Phe
 580 585 590
 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 595 600 605
 Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 610 615 620
 Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 625 630 635 640
 Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 645 650 655
 Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 660 665 670
 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 675 680 685
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 690 695 700
 Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 705 710 715 720
 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 725 730 735
 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 740 745 750
 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 755 760

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